Improving the Efficiency of Lifestyle Change Interventions for the Prevention of Cardiometabolic Disease

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SUMMARY

INTRODUCTION

If advising people about the health benefits of exercise and dietary restraint was enough to make them change their fattening lifestyles, ours would be a nation of fit and lean people.

While the knowledge about the causal correlation between physical activity, diet and health is ubiquitous in the population, pathogenic sedentism and over-alimentation remain the dominant way of life. They have been identified as the major and modifiable causes of today's epidemic of cardiovascular and metabolic diseases.

The paradox of behaving in a self-harming way, while being fully cognizant of the feared consequences, is the definition of addiction in other terms. At its core are neurohormonal mechanisms, which resist volitional attempts at behaving contrary to what these mechanisms impel the organism to do. The high attrition rates and nearly complete decay of adherence observed in lifestyle change interventions suggest that health behaviors are the result of autonomous drives, which frustrate volitional interference. The implication for research is to abandon the untenable precept of health behaviors being controlled exclusively by reason. Rather should research be focused on formulating models with which to explain the behavioral paradox, and from which to develop and test strategies for more efficient lifestyle change interventions. This is the aim of this study. It presents the case for a homeostatic feedback loop in which the organism's energy flux and energy reserves are the autonomous effectors of a drive to eat, the satisfaction of which necessitates considerable amounts of physical activity for the procurement of the food available at a distinct energy density in the organism's natural habitat. Shaped by natural selection to maintain energy homeostasis, this homeostatic feedback loop malfunctions in the recently emerged modern human environment, which lacks the obligatory physical activity cost of food, while presenting the latter in a processed form of high energy density to which the human organism remains unaccustomed. Runaway weight gain and overweight are the measurable consequences of this derailment. Based on these insights this work presents a strategy to reestablish energy homeostasis, by instituting a self-correcting cognitively controlled feedback loop with physical activity being the loop's output, and the weight perturbations, which result from its derailed autonomous archetype, being the loop's input. This cognitively controlled negative feedback system attempts to attenuate and reverse the runaway weight gain, not by a futile attempt to directly manipulate its causative derailed autonomous homeostatic system, but by decreasing or reversing the latter's effect on body weight.

This paper presents the rationale, the operationalization and the results of this work as well as the conclusions drawn therefrom.

THEORETICAL BACKGROUND

Essential to organic life is its ability to maintain homeostasis in the face of external challenges. Adequate strategies for the maintenance of energy homeostasis have been subject to natural selection, favoring genetic retention of those variants, which ensured survival under the given conditions of energy density of procurable food and the obligatory energy cost for its procurement. Today's environment dramatically differs from the one in which these mechanisms had been imprinted into the human genome. The physical activity cost, obligatory for food procurement in the natural pre-historic human habitat, has been all but abolished. Available food is being manufactured towards a substantially larger energy density. The negative feedback loops, which are the foundation of homeostatic balance, fail to operate under these conditions, leading to the progressive increases in body weight and body fat, which in turn initiate atherosclerosis as the causal pathogenic process underlying cardiovascular disease. With less than 10% of the adult population being free of the known risk factors for this disease, its economic burden is growing at a rate, which outperforms the growth of gross national products in developed nations.

Evidence from epidemiological as well as functional and morphological investigations overwhelmingly support the notion that physical activity correlates strongly with cardiovascular health. While the pathways of this causal correlation are not fully understood, the current body of knowledge suggests that physical activity's anti-inflammatory effect on the endothelial lining of the arterial tree is the major driver of this correlation. Endothelial cells respond to PA stimuli by maintaining or restoring the balance between pro-and anti-oxidative pathways, thereby maintaining or improving an anti-atherogenic vascular environment.

The curious fact, however, remains, that many people who are aware of the benefits of exercising regularly do not behave in accordance with their knowledge, and fail to adhere to exercise interventions, which they had entered voluntarily. Reports of drop-out rates of 50% within the first 6 months are frequently encountered in the literature, and almost complete reversal of risk factors to their baseline values within 3-5 years from commencement of clinical lifestyle change interventions is the status quo of institutionally organized behavior change efforts. Behavioral science has formulated a multitude of models explaining human behavior. Common to all models is the implicit assumption of volition as the final authority determining an individual's behavior. However, the evidence is overwhelming that there exists some autonomous behavioral drive with the power to override reason and volition. One ecological observation to that fact is the inability of obese children and adults to reduce their weight through voluntary behavioral change, despite the substantial and measurable agony load imposed onto them through societal, economical and health care discrimination.

The striking similarity of this health behavior paradox with behaviors of addiction is mirrored in the hormonal underpinnings observable in both behaviors. The investigations into the physiological correlates of feeding behavior, prompted by the insights from addiction research, suggest the presence of neuro-hormonal feedback loops with distinct orexigenic

and anorexigenic pathways. Coordinately they appear to drive an organism's feeding behavior in response to hormonal signals of energy reserves and of energy flux. These pathways have been subject to natural selection in an environment, which placed an obligatory physical activity cost before food acquisition and ingestion. That is, the drive to eat is primarily a drive to move-to-be-able-to-eat. The important implication of this view is that physical activity behavior is the organism's homeostatically controlled behavioral effector, rather than feeding *per se*, as is currently assumed by biomedical set-point models.

In the modern environment, which lacks the obligatory physical activity component of food acquisition, physical activity has been knocked-out of the homeostatic equation of which it forms an integral part. Inaccessible to rational override, humans find these autonomously operating behavioral drives to frustrate volitional efforts of modifying them for the prevention of the diseases, which are precipitated by these autonomous mechanisms' derailment.

The success of behavior change interventions is further constrained by their being typically designed along standardized strategies, which disregard the idiosyncrasies of their participants. Modeled around the paradigm of acute care, most, if not all, interventions are of a limited period only, after which the participants are left to their own devices. However, chronic conditions necessitate chronic care, and the abrogation of the obligatory physical activity cost of energy acquisition constitutes a chronic exposure of human homeostasis to a pathogen that requires chronic remedial measures.

Hence, efforts for the development and testing of alternative strategies, modeled around the effective principle of the feedback loop, are warranted. Its purpose is to entrain physical activity into a habitual response to specific cues.

METHODS

The review of evidence of the physiological and behavioral aspects of health behavior change suggests the need for an alternative approach to instituting lasting health behavior changes. With a view to the self-correcting feedback loop, which underlies and effectively ensures homeostasis in biology, it presents itself as the ideal model to be operationalized in health behavior change interventions. Continuous self-monitoring is the central principle, with the objective of constant actual vs. target assessment of behavior change results. Complemented by the principles of individualization and continuity, this strategy is hypothesized to yield (a) significant improvements of the adherence rate to a physical activity intervention compared to published results, and (b) a significant improvement of vital signs and risk parameters among the adherent participants, when compared to their non-adherent peers.

Hypotheses

Four hypotheses were tested in this intervention:

1. Adherence: the proportion of adherent participants will be 75% or better.
2. Significant improvement of cardiopulmonary fitness, expressed in peak oxygen consumption

3. Significant Improvement of parameters of weight status, expressed as body weight and BMI
4. Significant improvement of risk factors for cardiovascular disease, specifically blood lipids ad PROCAM risk score

No *a priori* hypothesis had been formulated with respect to comparison of the adherence rate with published adherence rates. The reason being that the principles applied in this intervention necessitate an adherence definition, which differs from those reported for other intervention trials. The improvements in hypotheses 2-4 refer to significant effects within the adherent group from baseline to follow-up, and between groups of adherent and non-adherent individuals.

Overall Study Design

The study was designed as a non-randomized intervention trial in which non-adherent subjects served as the controls. The restricted sample size of 120 participants, due to logistical and budgetary constraints, had sufficient power to detect the hypothesized effects. The 6-months intervention was performed at an electronics industrial estate in the South-Western German state of Baden-Württemberg, recruiting its participants from among the predominantly white-collar employees of the major corporate tenant at that estate. The study's target participants were sedentary adults aged 25 years and older with no physical or mental conditions, which would have prevented them from participating in an exercise program, or which would have exposed them to an elevated risk.

Ethics

Ethics approval for this study was obtained from the ethics committee of the state medical board of Baden-Württemberg, and informed consent was obtained from all participants prior to enrollment into the study.

Statistical Measures and Procedures

Analyses for differences between groups at baseline were performed using unpaired *t*-test and the Chi-square (χ^2) test for categorical data. Change from baseline to follow-up within groups were tested using paired *t*-test for continuous data, or the Chi-square test or Fischer's exact test for categorical data. Changes from baseline to follow-up were tested between adherence groups using the *t*-test for continuous data, and the Chi-square test for categorical data. Statistical significance was accepted at $p<0.05$. Two-by-two contingency tables were constructed to assess whether dichotomized change in parameter was related to adherence-group association. In the case of significant findings, odds ratios were calculated and their 95% CI were assessed using logistic regression.

Intervention Curriculum

All participants received a detailed personal appraisal of their baseline measurement results during a one-on-one consultation. Participants were then familiarized with the use of their web based electronic lifestyle file for monitoring and logging their physical activity and body weight

data. A minimum exercise curriculum of thrice weekly 20 continuous minutes of high intensity interval training was agreed to by all participants, with encouragement given for aerobic and/or resistance exercise to be performed in excess of this minimum requirement. The recommendations were based on each participant's health profile with a view to improving specific health parameters. Participants were encouraged to login on a daily basis into their electronic lifestyle file.

RESULTS

Adherence was defined as meeting all of the following three parameters: (a) Latency of last logged exercise of ≤7 days prior to follow-up, (b) weekly volume of ≥ 60 min of exercise, and (c) duration of ≥ 90 days (3 months) of consecutive weeks of logged exercise volume. This definition of adherence provides an answer to the question, what proportion of study participants adheres to the PA protocol at follow-up and has done so for durations and at physical activity volumes, which are expected to yield tangible health benefits.

Baseline Comparisons

Of the 117 participants (28.2% female) enrolled into this study, 89 (76%) met the adherence criterion. No significant differences of baseline parameters were found between adherent and non-adherent groups. Comparison with data published for the World Health Organization's MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) study of a comparable German urban population showed that the study participants had a significantly higher BMI compared to the population mean (28.7 vs. 27.3 and 29.3 vs. 26.9 for the male and female subgroups respectively), and a minimally but significantly better blood lipid profile in the male sub-group.

Hypotheses Testing

The group of 89 adherent participants had reported an exercise volume in excess of 2.5 times the baseline recommendation of 3x20 min weekly, with a median of 158 min.

The adherent participants significantly increased their mean peak oxygen consumption by close to 1 MET (from 32.8 to 36.1 ml/kg/min), whereas the 28 non-adherent participants witnessed a small but non-significant decrease (from 32.5 to 32.1 ml/kg/min). The between-group difference was significant with $p<0.001$.

While the non-adherent group significantly decreased their body weight and BMI (1.5 kg and 0.4 kg/m^2 respectively), the decrease in the adherent group was approximately 3 times larger (4.3 kg and 1.4 kg/m^2 respectively) and significantly different from the non-adherent group.

Of the lipid parameters, total cholesterol decreased significantly by 9 mg/dl ($p<0.001$) in the adherent group, and HDL increased significantly by 2.3 mg/dl ($p<0.01$) in the subgroup of adherent males. Small but non-significant increases of total cholesterol and decreases of HDL cholesterol were observed in the non-adherent group. The between group differences were significant with $p=0.02$ and $p=0.038$ for total cholesterol and HDL cholesterol respectively. The total cholesterol/HDL-cholesterol ratio decreased significantly by 0.2 units

from 4.2 to 4.0 in the adherent group with $p<0.001$ and increased non-significantly in the non-adherent group. In the sub-group of the 63 participants with baseline ratio in excess of 4, the ratio decreased significantly in the adherent group by 0.4 units from 5.0 to 4.6 ($p=0.001$), with a small but non-significant increase in the non-adherent group from 5.0 to 5.1. Between-group difference was significant with $p=0.01$.

Significant reductions were found for diastolic blood pressure of 5.9 and 5.3 mmHg in the non-adherent and adherent groups respectively, with no significant changes in systolic pressures. Since blood pressure correlates with body weight change rather than with changes of physical activity and cardiopulmonary fitness, the subgroup of participants who had entered the study with a BMI>25 and a systolic and/or diastolic pressure in excess of 129 or 84 mmHg respectively were dichotomized into those having achieved a weight reduction of at least 1 kg vs. those who did not. The weight-reducing group witnessed a significant reduction of systolic and diastolic pressures of 4 and 10 mmHg respectively ($p<0.01$), whereas non-weight-reducing participants showed a small significant decrease of 3 mmHg of diastolic pressures, with no significant change in systolic pressure. Between-group differences were significant with $p<0.05$.

Adherent participants showed a significant 14.7% reduction of PROCAM risk score vs. a 16.6% non-significant increase in the non-adherent group. Between-group difference was significant at $p<0.01$.

DISCUSSION

The study results favor the hypotheses of a 75% proportion of adherent subjects (N=89) at the end of the intervention. In this study, the term adherence does not relate simply to the volume or duration of PA. The adherence definition of latency, volume and duration of the physical activity habit considers as adherent only those subjects whose changed physical activity habit is (a) operational at follow-up, and (b) has been operational for a long enough period und with a large enough exercise volume to yield significant and clinically relevant improvements of vital signs which are indicative of cardiovascular health. This substantially different way of defining adherence, which emerges from the theory and model underlying this intervention strategy, complicates comparison with adherence rates published for other studies.

The substantial increase of physical activity volume over the minimum recommended level in the adherent group also favors the contention that engaging a cognitive feedback loop stimulates participants to increase the volume of their physical activity as the loop's effector. This increase is reflected in the substantial and significant increase of cardiopulmonary fitness of 1 MET, which has been found to correlate with a substantial decrease of cardiovascular disease risk.

Equally relevant were the observed reductions in body weight status with an odds ratio of 8 (adherent vs. non-adherent subjects) for reducing body weight by ≥5% vs. reductions of less than 5% in overweight and obese subjects. This bespeaks a strong effect, given the relatively

short observational period of 12 weeks within the 6-months intervention. A minimum weight loss of 5% has been suggested to be required for clinically relevant hormonal improvements.

Of the lipid markers, only the ratio of total cholesterol to HDL cholesterol emerged as being not only significantly improved but also to a clinically relevant extent. However, given the acknowledged superiority of this ratio over individual lipid fractions as predictive biomarkers, the intervention has demonstrated a clinically relevant improvement among adherent participants.

The proportion of adherent participants, who had reduced their PROCAM risk score by at least 10% was nearly 3 times the proportion of non-adherent subjects achieving the same reduction (58.9% vs. 20%). This result supports the notion that this intervention can be benchmarked with a risk assessment tool, which is commonly used in clinical practice.

CONCLUSIONS

The recognition that (a) autonomously operating homeostatic feedback loops drive the human feeding behavior, of which (b) physical activity is an inextricable component, provides for an effective reformulation of behavior change strategies to correct the runaway weight gain, which results from modern environmental derailment of the homeostatic feedback loop.

While volitional attempts to interfere with autonomously driven behaviors have remained frustratingly ineffective, the results of this study suggest that volition is an effective operator of a self-correcting feedback loop. When the latter gears into the evolutionary human system of energy homeostasis, accepting as its input the weight gain resulting from its homeostatic archetype's derailment, volition is potentially more effective at arresting and reversing pathogenic weight gain than when attempting to directly modulate autonomously driven health behaviors.

Taken together, the results of this study favor the hypothesis that an activated cognitively controlled feedback loop for the correction of weight perturbations, yields significant and clinically relevant improvements of cardiometabolic risk parameters.

Condensed into one sentence:

It may be more important to correct a person's bio-behavioral malfunction that manifests in disease, than to correct the physiological malfunction with which the disease manifests.

DEFINITIONS AND ABBREVIATIONS

DEFINITIONS

When referred to in comparison to other study populations, the subjects of this study are referred to as the ELF sample, based on the naming chosen for the underlying intervention tool (the electronic lifestyle file, ELF).

In the context of this work, the following terms shall have the ascribed meanings:

Atherosclerotic Vascular Disease (AVD)

refers to the cardiovascular diseases (CVD) resulting from atherosclerosis (coronary heart disease, cerebrovascular disease and peripheral arterial disease).

Cardiometabolic disease

refers to the atherosclerotic vascular diseases (AVD) and type 2 diabetes mellitus (T2DM).

The rationale for combining both diseases into a disease cluster is provided by the existence of common pathways, specifically low-grade inflammation, insulin resistance and endothelial dysfunction [1]. The phenomenon of shared pathways has very recently been confirmed in a genetic-based investigation into disease relationships and their pathways [2]. The study's finding that hypertriglyceridemia, hypercholesterolemia, hypertension, atherosclerosis and T2DM are among the top 20 connected diseases vindicates earlier efforts to recognize "*a cluster of metabolic risk factors for cardiovascular disease and T2DM"* as the metabolic syndrome X (definition, in italics, taken from the vocabulary of Medical Subject Headings, MeSH).

With this recognition the use of the term cardiometabolic disease or cardiometabolic syndrome has become accepted [3].

Endothelial Dysfunction

refers to the impairment of important endothelial functions, including anticoagulant, vasodilatory and anti-inflammatory properties [4].

Physical Activity and Fitness

The following definitions are in line with those formulated in the Physical Activity Guidelines Advisory Report of 2008 [5].

> *Exercise*
>
> refers to physical activity that is carried out at an individual's discretion, that is not essential to the tasks of daily living and which is performed with the intent to maintain or improve physical health or fitness.

Cardio-Respiratory Fitness (CRF)

refers to the ability of the circulatory, respiratory and muscular systems to take-up, transport and use oxygen during sustained physical activity. The objective measurement parameter is maximal oxygen uptake ($VO2_{max}$).

Maximal Oxygen Uptake ($VO2_{max}$)

refers to the body's capacity to take-up, transport and use oxygen during a maximal exertion involving dynamic contraction of large muscle groups.

Peak Oxygen Uptake ($VO2_{peak}$)

refers to the highest oxygen uptake observed in an individual during a graded maximal exercise test. $VO2_{peak}$ may equal $VO2_{max}$ or may remain below, depending on attenuating circumstances such as cooperation of the individual or discontinuation of the exercise test due to the occurrence of symptoms suggesting increased health risk.

Body Cell Mass (BCM)

refers to that component of lean body mass which consists of muscle and organ tissue.

Use of personal pronouns, whether male or female, are not to be construed as implying gender bias. For reasons of readability, I have used one or the other, without any derogatory or biased intent.

ABBREVIATIONS

ACLS	Aerobic Center Longitudinal Study
ACSM	American College of Sports Medicine
AHA	American Heart Association
AIB	Appetitive Ingestive Behavior
apoE	apo-lipoprotein E
AT	Anaerobic Threshold
ATP	Adenosine Triphosphate
ATP III	Adult Treatment Panel III
AVD	Atherosclerotic Vascular Disease
BCM	Body Cell Mass
BIA	Bio-Impedance Analysis
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body Mass Index
CASS	Coronary Artery Surgery Study
CDC	U.S. Centers for Disease Control and Prevention
CFL	Cognitively Controlled Feedback Loop
CFL+	operant CFL at follow-up (identifying adherent subjects)
CFL-	no CFL present at follow-up (identifying non-adherent subjects)
CHD	Coronary Heart Disease
CI	Confidence Interval
CIB	Consummatory Ingestive Behavior
CPET	Cardio Pulmonary Exercise Testing
CRF	Cardio-Respiratory Fitness
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DLW	Doubly Labeled Water
EC	Endothelial Cell
ED	Endothelial Dysfunction
EDRF	Endothelial Derived Relaxation Factor
EGIR	European Group for the Study of Insulin Resistance
ELF	Electronic Lifestyle File
EMT	Error Management Theory
eNOS	endothelial Nitric Oxide Synthase
FRS	Framingham Risk Score
GUTS	Growing Up Today Study
HAPA	Health Action Process Approach
HBM	Health Belief Model
HDL	High-Density Lipoprotein
HEPA	Health Enhancing Physical Activity
HF	Heart Failure
HIT	High Intensity Interval Training
HPA	Hypothalamus-Pituitary-Adrenal

hsCRP	high-sensitivity C-Reactive Protein
HWE	Healthy Worker Effect
IDF	International Diabetes Federation
IDL	Intermediate-Density Lipoprotein
IL	Interleukin
iNOS	inducible Nitric Oxide Synthase
IQR	Interquartile Range
IST	Incentive Sensitization Theory
KIHDS	Kuopio Ischaemic Heart Disease Risk Factor Study
LDL	Low-Density Lipoprotein
Lept	Leptin
LTPA	Leisure Time Physical Activity
MCC	MONICA Collaborating Center
MeSH	Medical Subject Headings
MET	Metabolic Equivalent
MetS	Metabolic Syndrome
MONICA	Multinational **MONI**toring of trends and determinants in **CA**rdiovascular disease
NLM	National Library of Medicine
nNOS	neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NPY	Neuropeptide Y
NWCR	National Weight Control Registry
OR	Odds Ratio
PA	Physical Activity
PAGAC	Physical Activity Guidelines Advisory Committee
PARS	Physical Activity Referral Scheme
PMT	Protection Motivation Theory
PROCAM	Prospective Cardiovascular Munster Study
PVD	Peripheral Vascular Disease
QoL	Quality of Life
REE	Resting Energy Expenditure
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
SCT	Social Cognitive Theory
SD	Standard Deviation
SICAM	Soluble Intra-Cellular Adhesion Molecule
SO	Superoxide
SOD	Superoxide Dismutase
T2DM	Typ 2 Diabetes Mellitus
TCH	Total Cholesterol
TG	Triglyceride
TOMHS	Treatment Of Mild Hypertension Study
TPB	Theory of Planned Behavior

TRA	Theory of Reasoned Action
TTM	Transtheoretical Model of Behavioral Change
ULSAM	Uppsala Longitudinal Study of Adult Men
VCAM	Vascular Cell Adhesion Molecule
VO2max	maximal Ventilatory Oxygen Consumption
VO2peak	peak Ventilatory Oxygen Consumption
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

INTRODUCTION

The aim of studies on physical activity interventions for the prevention of chronic disease is to reduce its prevalence in our populations.

The paradigm underlying most, if not all, such studies is the unsinkable belief in reason and volition as the drivers of adherence to physical activity interventions. Neurohormonal evidence, however, points to a human model of energy homeostasis in which feeding and physical activity behaviors are subject to autononomous control mechanisms, inaccessible to a rational override. While this view may be unintuitive and uncomfortable for the reasons discussed hereinafter, it holds the key to materially increasing the prevalence of health-enhancing lifestyle behaviors. The frustratingly low adherence rates to the latter necessitate the development of a new approach that is firmly grounded in a new paradigm evolving from neurohormonal evidence. This dissertation responds to this need, as well as to the call which has been made to shift research efforts from effectiveness towards dissemination studies [6].

The section *Theoretical Background* discusses the lifestyle origins of cardiovascular disease and the evidence for physical activity as an effective means for its prevention.

This section also presents the evidence for physical activity and dietary behaviors being driven by neurohormonal states, which are inaccessible to mental faculties other than self-observation. A working model is proposed for the understanding of health behavior (physical activity and dietary) as the phenotypical representation of autonomously controlled neurohormonal feedback loops which evolved from natural selection.

The *Methods* section discusses the implications of this model for successful behavior change strategies and the three essential aspects of an effective behavior change intervention are presented: individualization, monitored self-monitoring and continuity. This section closes with the development of 4 hypotheses for testing the model in an exploratory intervention:

(1) the intervention will yield an adherence rate of 75%
(2) adherent subjects will show a significant and clinically relevant increase in cardiorespiratory fitness
(3) adherent subjects will benefit from improved parameters of body weight status
(4) adherent subjects will reduce their risk for cardiovascular disease events

The *Results* section presents the results of this exploratory study investigating the hypotheses developed in the preceding sections.

The *Discussion* section discusses the results and the evidence in support of the hypotheses 1-4, as well as the arguments for extending this research to investigate the applied tool's ability to engage a cognitively self-correcting feedback loop for reestablishing energy homeostasis in its adherent user.

THEORETICAL BACKGROUND

"No biological problem is solved until both the proximate and the evolutionary causation has been elucidated." Ernst W. Mayr

THE EVOLUTIONARY PERSPECTIVE

"Move or die" is a rule that applies to all vertebrates and probably has shaped their genomes.

Be it the need to acquire food, to avoid becoming it or to deal with threats and challenges, modern society's lack of the need for physical activity is, in evolutionary terms, a very recent phenomenon of the past 200 years [7].

The resulting high prevalence of sedentary lifestyles strongly associates with the emerging epidemic of cardiometabolic diseases, site specific cancers and musculoskeletal disorders [8]. Consequently, it has been suggested that the human genome, having been programmed for substantially higher levels of physical activity, is inadequately equipped to maintain health and function on the cellular and tissue level when confronted with hypokinetic lifestyles [8, 9]. This mismatch between genome and environment disturbs or derails human functional homeostasis, the sequelae of which have been termed "syndromes of impaired genetic homeostasis" by Neel [10]. It is the model which supersedes the author's original 1962 theory of the thrifty genotype [11]. Essential to it is the interaction between the three mutually dependent elements, which define an organism: its genotype, its phenotype and its environment.

It is based on the rationale that:

(1) Feeding and physical activity behaviors have been subject to a process of natural selection, favoring genetic retention of those behavioral variants which ensured survival under the given conditions of energy density of procurable food and the obligatory energy cost for its procurement.

(2) Sudden, profound and prevailing changes of these aspects of energy cost and supply, to which the organism finds itself genetically unaccustomed, will challenge the organism's evolved ability to establish and maintain energy homeostasis with potentially pathogenic consequences.

(3) Reestablishing homeostasis will arrest or reverse the pathogenic process, consequently preventing overt disease and thereby substantially improving public health.

To this end, Neel explicitly suggested a euphenic strategy, a term introduced, to the best of my knowledge, by Lederberg in 1963 [12]. Euphenics may be defined as the science of improving the human phenotype after birth. But applying a 5-dollar word (euphenics) to a 50-cent concept (exercising more and eating less), does not solve the 50-cent problem, namely how to get people to adhere to a more physically active and dietary less indulgent lifestyle.

Despite the common knowledge about the detriments of sedentism and hyperalimentation, adherence to sufficiently physically active lifestyles remains frustratingly low [13, 14]. That this is commonly blamed on lack of willpower bespeaks a human self-perception of being a species capable of, and behaviorally driven by, rational thought [15]. However, as I will outline hereinafter, an accumulating body of evidence suggests (a) the existence of strong autonomous neurohormonal mechanisms which drive human physical activity and dietary behaviors, and (b) the inaccessibility of these drives to rational interference.

While these observations perfectly align with the aforementioned concept of energy homeostasis, they rub against the intuitive view of human health behaviors having rational rather than instinctive origins.

However, the formulation of effective behavior change strategies will depend on the underlying model's accuracy, not on its appeal. As the disregard for autonomously operating behavioral drives has failed public health efforts to stem the tide of lifestyle disease, the development of a new paradigm of human health behavior is warranted.

Consequently I propose to develop intervention strategies from a modified model of human energy homeostasis, which aligns with evolutionary principles, specifically the objective of acquiring and maintaining sufficient energy levels to ensure the organism's survival and reproduction. At the core of this model are autonomously driven physical activity and feeding behaviors which operate as the effectors of a negative-feedback loop that has been shaped by natural selection to establish energy homeostasis under the prevailing environmental conditions of (a) a relatively low energy density of the food available to the organism and (b) an obligatory physical activity cost for food acquisition. This integration of all the three elements which determine an organism's phenotype, namely its genome, its behavior and its environment, achieves three important goals: *Firstly*, it reconciles with the observed phenomenon of energy homeostasis in all organisms which live in their natural habitat, including ancestral and some contemporary humans. *Secondly*, it explains how the sudden environmental shift from low to high energy density of food and the elimination of the physical activity cost for its acquisition derails this feedback loop, which has, over the course of evolution, been genetically programmed to maintain energy homeostasis under reverse environmental conditions. *Thirdly*, it provides for the formulation of testable hypotheses about interventional strategies with which to re-establish energy homeostasis within the prevailing modern human environment.

Proof of concept for a disturbed metabolic homeostasis is the observation of progressively increasing body weight and body fat in our developed societies [16-20], which has colloquially been termed the obesity epidemic. The latter reflects substantial changes in dietary habits, which evolved secondary to the industrialization of food production, storage and distribution.

That this ecological weight gain comes with an apparent bias to preserve fat mass, even in intended weight loss, supports the notion of an evolutionary trait that is maladaptive to the novel environment. Evidence for this bias has very recently emerged from an elegant

experiment that elucidated the relative contribution of body and organ mass loss to reductions in resting energy expenditure (REE) following diet-induced weight loss in 45 overweight and obese women [21]. The loss of fat-free mass, fat mass and organ mass explained only 60% of the observed reduction in REE. The remaining 40% were due to an adaptation in thermogenesis. From an evolutionary point of view such a bias protects energy reserves, thereby helping the individual to survive in an environment of unpredictable food supplies, the acquisition of which demands considerable energy expenditure.
Only the obese modern human may not consider this evolutionary principle very helpful to her attempts at achieving a more healthy body weight.

If, as has been suggested, sedentism is the common denominator of disturbed energy homeostasis [22] and chronic cardiovascular disease (CVD) [9, 23], physical activity will be linked to the pathogenesis of CVD, from its early and asymptomatic atherosclerotic antecedent to its overt disease endpoints. Interestingly, atherosclerotic lesions, have been histologically confirmed in 3,500 years-old Egyptian mummies, in accidentally mummified 400 years-old bodies of Alaskan Eskimos, and in 18th century mummies of the Aleutian islands [24, 25]. Obviously, PA did not necessarily prevent this precursor of cardiovascular disease in our ancient forebears. But would their high physical activity levels have protected them against developing the cardiovascular complications that plague us in epidemic proportions today? We can't say, because our ancestors simply may not have lived long enough for atherosclerotic and diabetic endpoints to manifest in epidemic proportions:

> While the life expectancy in today's longest lived female cohorts is around 85 years, until the mid 1800s it was still just 45 years [26]. And the average lifespan of pre-agricultural humans appears to have been less than 30 years [27]. In these age groups, symptomatic manifestations of the cardiometabolic disease spectrum are not very prevalent.

However, the fact that physical activity and its closest correlate, physical fitness, are powerful determinants of arterial health and health in general, is supported by an accumulating body of evidence. Before reviewing this evidence it is worthy to reflect on the extent of the burden of cardiometabolic disease.

THE BURDEN OF DISEASE

Cardiometabolic disease has become the leading cause of mortality and morbidity [28] in developed and developing nations. It is the single largest contributor to health care expenditure [29], the latter now growing 70% faster than GDP across OECD countries [30, 31].

The U.S. 'Public Health Action Plan to Prevent Heart Disease and Stroke' posits that there will be no reversal of the epidemic of cardio-metabolic disease without more effective prevention [29]. This plan has become a corner stone of the Healthy People 2010 initiative [32]. However, the desired reduction in cardiometablic disease is threatened by a recently

observed trend of a decreasing prevalence of low-risk factor status, at least in the U.S. population [33]. Only 1 in 12 adult Americans currently meets the 5-criterion low-risk profile, which has been defined as (1) not currently smoking, (2) total cholesterol <5.17 mmol/L (<200 mg/dL) and not using cholesterol-lowering medications, (3) systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg and not using antihypertensive medications, (4) BMI <25 kg/m2, and (5) not having been previously diagnosed with diabetes.

The prevalence of low-risk status is now on a decrease from its peak in the late eighties. While the future impact of this trend on cardiovascular health cannot reliably be extrapolated, the three factors responsible for the reversal, specifically blood pressure, diabetes and BMI are all well correlated with the complications of atherosclerosis. After all, in 60% of the cases of sudden coronary death, acute luminal thrombosis from vulnerable atherosclerotic plaque is the triggering event, and total atherosclerotic occlusion accounts for the majority of the remaining 40% [34].

The current (2007) prevalence of adolescent overweight in the U.S. translates into cumulative direct and indirect morbidity- and mortality-related costs for coronary heart disease (CHD) for the period 2020-2050 of between 43” to 63” Billion U.S.$, depending on which treatment scenario is applied [35]. The most frustrating aspect of this crystal-ball gazing exercise is probably not the mind staggering figure, but the fact that the sum total of indirect and direct medical cost will only marginally benefit when the most aggressive treatment procedures are applied [35].

That is, the benefit in indirect costs is almost fully wiped out by the extra treatment cost.

PHYSICAL ACTIVITY PREVENTS CARDIOMETABOLIC DISEASE, BUT WHAT PREVENTS PHYSICAL ACTIVITY? A REVIEW OF THE SCIENCE

The Physiological Aspects: Physical Activity Prevents Cardiometabolic Disease

The following is a review of the epidemiologic as wells as physiologic evidence for the association between physical activity, its close correlate physical fitness and cardiovascular health.

The Epidemiological Evidence

Physical activity has been widely recognized to lower diabetes risk [36] as well as cardiovascular morbidity and mortality [23, 37]. Specifically, the impact of physical activity on the traditional risk factors for atherosclerotic vascular disease has been well documented [38].

Just a year ago, the U.S. Physical Activity Guidelines Advisory Committee (PAGAC) summarized the currently available evidence for a correlation between physical activity and morbidity and mortality [5]. The 73 reviewed studies covered more than 830,000 men and women aged 16 years and older, who were predominantly recruited from apparently healthy

populations. The median follow-up was 12 years and the median reduction of relative risk between the most and least active groups was 31% with no significant difference between the genders.

Consequently, PA has become a cornerstone of governmental recommendations for prudent lifestyles [39].

These epidemiological evaluations fail to answer the important question, through which pathways PA affects health. In a most convenient scenario, the effects of PA on morbidity and mortality should be reflected in the biomarkers used to measure risk. However, there is compelling evidence for PA to modify risk independently, that is, via pathways, which have yet to be elucidated and which do not necessarily affect traditional biomarkers of risk.

Physical Activity As An Independent Modifier Of Health Status

When compared to their sedentary peers, engaging in vigorous-intensity exercise, at least thrice per week, associated with a 50% reduced 6-year mortality rate in cancer patients registered in the Scottish Health Survey [40].

In a 15-year follow-up of 25,000 patients of the U.S Coronary Artery Surgery Study (CASS), those participants, who reported vigorous physical activity, had a significantly lower mortality rate than their sedentary peers [41]. This relation remained significant even after adjusting for age, gender, smoking status, hypertension, diabetes, body mass index, left-ventricular ejection fraction and serum total cholesterol.

A study of 2,678 elderly men of Japanese extraction in the Honolulu Heart Program demonstrated that those whose daily walking distance was less than 400 meters had twice the risk of fatal and non-fatal CVD compared to those who walked in excess of 2.4 km per day [42]. This risk ratio was unaffected by adjustments for the conventional risk factors age, total and HDL cholesterol, hypertension, diabetes, alcohol use, performed physical function score, and number of years lived in Japan during childhood, as well as for the use of beta-blocking medication, aspirin and insulin.

In the Harvard Alumni Study of 12,516 middle-aged and elderly men, those whose estimated weekly energy expenditure through exercise exceeded 1,000 kcal showed a significant and substantial risk reduction for CVD mortality and morbidity across all risk factors and their combinations [43].

Physical Activity As An Effect Modifier In Obesity

An investigation into physical activity as an effect modifier of the correlations between BMI, fat and fat-free mass and all-cause death was conducted in a randomly selected middle-aged subgroup of the Danish MONICA population [44]. Among the men of the 2,800 participants, physical activity abolished the U-shaped relationship between BMI and 13-year mortality observed among sedentary men. While in women there was no statistically significant relation

between BMI and mortality, the physically active normal-weight women (BMI 19-24.9) enjoyed the lowest mortality rate.

In a somewhat older cohort of 37,000 Swedish men, followed over 10 years, the elimination of BMI-associated risk elevation observed in the active Danish men could not be replicated [45]. However, when compared to lean active men, the relative risk of obese active men tended to be lower than that in lean inactive men.

A similar effect was observed in a 10-year prospective study of the 185,000 male and female participants of the U.S. National Institutes of Health-AARP Diet and Health Investigation [46]. Using the most active normal-weight (BMI 18.5-<25) participants as the reference group, similarly active participants with a BMI between 30 and 35 had the same hazard ratio (1.62) for all-cause mortality as the sedentary normal-weight group.

In a selection of over 21,000 women from the Women's Health Study, PA showed a strong inverse association with CVD risk independently of the observed correlation between BMI and disease risk [47].

Physical Activity And The Compression Of Morbidity

PA appears to contribute to a compression of morbidity, as observed in the reduced need for hospital care and nursing home care in the last year of life. In a Finnish study of 846 persons aged 66 and above, the risk for all-cause hospital care was halved in the men classified as continuously physically active from middle age onwards, when compared to their least active peers [48]. The same degree of risk reduction was observed for nursing home care in women.

In a study of the very old (aged 70-88), those who had been physically active in their seventies were substantially more likely to be functionally independent at age 85 [49].

Physical Activity And Genetics

The FinTwin16 study investigated the ability of PA to attenuate the genetic influence on BMI and waist circumference [50]. The results show that the genetic factors on BMI and waist circumference are less dominant in physically active subjects, indicating that particularly those with a genetic predisposition for obesity would benefit from increased levels of PA.

These results were confirmed in the Danish-Finnish GEMINAKAR study of over 1,000 complete twin pairs [51]. The study demonstrated that a high level of physical activity moderates the genetic variation in weight and waist circumference, which again suggests that even in individuals who are genetically predisposed to obesity, physical activity may moderate the adiposity risk.

In a recent attempt to calculate the potential of preventing or postponing death from heart disease by means of a hypothetical delivery of perfect primary preventive care, PA appeared

as the single largest contributor, followed by prudent dietary habits and abstinence from tobacco use [52].

Morphological And Functional Evidence

While the epidemiological evidence for an inverse association between PA and cardiovascular health is persuasive, our knowledge about the biological effects of PA on CVD risk remains incomplete. However, the emerging understanding of the pathogenesis of CVD provides some important insights into the mechanisms by which PA exerts its protective role.

The Inflammatory Origin Of Cardiovascular Disease

Inflammation has begun to emerge as one such potentially important mechanism. In an 11-year follow-up of over 27,000 apparently healthy women of the Women's Health Study the inverse PA-to-CVD-risk association was explained to almost 60% by PA's effect on traditional and known risk factors [53]. Of these, the markers of inflammation (high-sensitivity C-reactive protein (hsCRP), fibrinogen, soluble Intracellular Adhesion Molecule 1 (sICAM-1)) made the single largest contribution.

These epidemiological observations align elegantly with the recently emerging understanding of atherosclerosis being an inflammatory disease rather than a disease of lipid deposition [54]. Approximately 50% of all atherosclerotic patients do not show the hallmark of disturbed lipid metabolism: hypercholesterolemia [55]. Also two thirds of all first cases of non-fatal and fatal CVD occur in individuals who do not meet the diagnostic criteria of the metabolic syndrome (MetS) [56, 57], which contains hypercholesterolemia and/or hypertriglyceridimia as a component criterion in all the 4 currently used sets of criteria as variably proposed by the World Health Organization (WHO), the International Diabetes Federation (IDF), the Adult Treatment Panel III (ATP III), and the European Group for the Study of Insulin Resistance (EGIR) [58]. In patients with the MS the risk for future peripheral vascular disease (PVD), however, is largely mediated through inflammation and endothelial dysfunction [59].

Hence, a new understanding of atherosclerosis as an inflammatory disease has replaced the previous emphasis on dyslipidemia as its primary cause [60, 61].

If atherosclerotic vascular disease (AVD) is mediated through inflammatory pathways, PA's cardioprotective value may well be the result of an anti-inflammatory effect.

A 2005 review of cross-sectional and longitudinal investigations concludes that PA owes its cardioprotective effect largely to the lasting anti-inflammatory response of the organism to chronic exercise challenge [62].

Further evidence for the PA-inflammation association comes from longitudinal, interventional and cross-sectional investigations. In a study of 3,810 elderly men, aged 60-79 after a 20-year follow-up, strong and inverse relations were observed between markers of inflammation and coagulation and PA levels at follow-up [63]. The strength and significance of these

associations remained unaffected by controlling for prevalent CVD, smoking status and obesity.

Exposure to a 6-months PA intervention yielded a significant reduction of inflammatory status in 60 T2DM patients irrespective of weight-loss [64].

In a recent cross-sectional observation of a middle-aged healthy 800-strong subpopulation of the German MONICA study, PA showed a strong and inverse relation with the inflammatory markers fibrinogen, CRP and Interleukin 6 (IL-6) [65]. These associations remained strong after adjustment for Body Mass Index (BMI), Waist-to-Hip ratio (WHR), smoking status, hypertension, diabetes and total-to-HDL cholesterol ratio. Specifically smokers and ex-smokers benefited the most from PA.

Evidently, the case for an association between inflammation, atherosclerosis and PA is compelling.

In the following section I attempt to merge these lines of evidence into a coherent view of AVD as an inflammatory disorder and PA as its anti-inflammatory remedy.

Genesis Of The Atherosclerotic Plaque

Among the initial steps of atherosclerotic lesion formation is the production of vascular cell adhesion molecules (VCAM), soluble intracellular cell adhesion molecules (sICAM) and other chemoattractant proteins, which promote leukocyte (specifically monocytes and T-lymphocytes) adhesion to the endothelial cell [66, 67]. Monocytes then penetrate the endothelial lining, where they differentiate into macrophages, engulf modified lipoproteins and mature into lipid laden foam cells [68].

These are the early manifestations of atherosclerotic fatty streaks, a process which begins early in life and which may already be clinically manifest in life's second decade [69, 70].

While the aforementioned biochemical reactions are characteristic for atherogenesis, they are fundamentally not different from other inflammatory responses to tissue injury. The purpose of inflammation is the removal or inactivation of the injurious cause. If this cause, however, persists, the ensuing fibroproliferative response may alter the morphology and function of the affected tissue, which is what we observe in typical chronic inflammatory diseases, such as cirrhosis of the liver, rheumatoid arthritis, renal glomerulosclerosis, pulmonary fibrosis and, *q.e.d.,* in atheroslcerosis [67]. It is this inflammatory response, which dominates atherogenesis throughout its disease stages.

Obviously, it is difficult, if not impossible, to directly observe plaque genesis in any given individual over the 3-4 decades, which it takes for an early fatty streak to mature into an initiator of an acute coronary event. However, a morphological classification scheme has been developed which allows the determination of risk, based on plaque characteristics [71].

In this scheme, the event most often liable for an acute coronary event is thrombus formation secondary to the rupture of the fibrous cap that covers mature atherosclerotic lesions [72]. In

these "fibrous cap atheromata" a layer of smooth muscle cells and collagenuous tissue separates the lipid core from the luminal blood flow. Once this protective layer becomes compromised, the risk of platelet aggregation, thrombosis and its consequences are high. While a differentiation is being made between ruptured plaque and plaque erosion as the thrombosis triggering events, our current understanding of their etiology remains fragmentary.

Today's consensus view, though, is that (a) atherosclerosis develops over 4-5 decades before becoming symptomatic [73], (b) inflammatory processes operate throughout all stages of disease progression [74], and (c) distinct types of atherosclerotic lesions exist which correspond to distinct disease stages and which associate with different degrees of risk for terminal events [75]. It is now also widely accepted that a dysfunctional endothelium, unable to maintain the necessary anti-inflammatory, anti-coagulant and vasodilatory properties that protect the vasculature from atherosclerotic insult [76], is the initiator of plaque development [67].

Correspondingly, disturbances to these endothelial functions have been termed endothelial dysfunction (ED), which is now thought of as the central mechanism underlying the initiation and progression of atherosclerosis [4].

Before examining the effects of PA on ED and atherosclerosis, it is worthy to briefly review the mechanisms that are instrumental in endothelial dysfunction.

The current body of knowledge supports a reduced production or bioavailability of nitric oxide (NO), a member of the reactive nitrogen species (RNS) and formerly known as endothelium derived relaxation factor (EDRF), as the main mechanism underlying ED.

The necessity of a functional endothelium for vasodilation to occur had (accidentally) been discovered and described in 1980 by Furchgott et al. [77]. Subsequent research efforts identified the gaseous nitric oxide molecule as the vasoactive substance [78, 79]. In our current understanding, the role of NO extends to inhibiting platelet aggregation [80], leukocyte adhesion [81] and vascular smooth muscle cell proliferation [82].

NO is produced by nitric oxide synthase (NOS) of which three major isoforms are known: eNOS – endothelial nitric oxide synthase; nNOS – neuronal nitric oxide synthase; iNOS – inducible nitric oxide synthase [83]. Both nNOS and eNOS are constitutively expressed in many cells, not only the ones from which they derive their names. However, iNOS is inducibly expressed in activated macrophages [83].

To a large extent, our understanding of the role of NOSs in atherosclerotic disease originates from experiments with genetically altered mice, in which either a NOS gene or the gene expressing apolipoprotein E (apoE) or both have been knocked out. ApoE is a necessary ligand for hepatic absorption of intermediate density lipoprotein (IDL) and of chylomicron remnants prior to their metabolization to LDL [84]. Consequently apoE dysfunction leads to elevated circulating cholesterol levels promoting atherosclerotic plaque formation.

The apoE/eNOS double knockout mice develop atherosclerosis substantially faster and with a larger yield of plaque than apoE knockout mice living under similar dietary conditions [85]. From these experiments it has been suggested that reduced bioavailability of NO, secondary to an impairment of eNOS function, promotes and accelerates the progression of atherosclerosis.

However, the association between NO and atherosclerotic disease is not as simple and straightforward as these experiments suggest. Knocking out the iNOS instead of the eNOS gene produces atherosclerotic lesions in apoE/iNOS double-knockout mice which are significantly smaller than those in comparable apoE knockout mice [86]. The fact that eNOS produces low amounts of NO whereas iNOS, expressed in response to inflammatory processes in macrophages, endothelial and smooth muscle cells, generates large amounts of NO, has led to the hypothesis that it is the net concentration of NO at the tissue level which determines whether it is of physiological or pathological consequence [87].

In support of this hypothesis is the observation that excessive iNOS activity in the macrophages of existing atherosclerotic lesions facilitates the production of the oxidant peroxynitrite resulting from an NO reaction with superoxide (SO), a member of the reactive oxygen species (ROS). This cascade promotes the oxidation of LDL, thereby aggravating the inflammatory response [88].

In this scheme, the reaction of NO with SO to form peroxynitrite, plays a central role. Peroxynitrite is a powerful agent for tyrosine nitration, which generally leads to a loss of function of the nitrated protein [89]. If that protein happens to be superoxide dismutase (SOD), the primary scavenger and inactivator of SO [90], the resulting increase in SO concentration may further exacerbate the production of peroxynitrite, indicating that it is the balance between NO and SO which determines whether the downstream consequences are protective or detrimental to the tissue [91].

In vitro experiments have demonstrated that the oxidation of lipids caused by peroxynitrite resulting from the reaction of NO and SO can be completely halted if the 1:1 substrate ratio is sufficiently shifted in favor of NO, as it effectively inhibits lipid peroxidation [92]. Put simply, while NO in reaction with SO produces a generally detrimental substance, peroxynitrite, a relative increase in NO keeps these detrimental effects in check. Or phrased another way: At any given concentration of SO, a relatively low SOD activity will leave proportionally more SO molecules ready for reaction with NO to form peroxynitrite. Hence, an increase in SOD activity, will reduce peroxynitrite formation thereby alleviating nitrosative stress while at the same time leaving a higher concentration of NO to amplify its physiological effect.

Given these insights, optimal preventive or curative intervention would first require an analysis of this NO/SO imbalance to (a) determine whether an impairment of NO or SO production is the cause, and in which tissue compartment the imbalance occurs, and to (b) administer the appropriate corrective treatment. However, our knowledge is currently

insufficient to disentangle the complexities of the ROS/RNS pathways for the development of interventions to effectively prevent or cure AVD [91].

What we do know is that the restoration and maintenance of physiological ROS/RNS function is an important goal in the prevention of atherosclerosis and its complications. Which leaves the question: is there any evidence to suggest that PA contributes to the structural and functional integrity of the endothelium, and thereby stabilizes atherosclerotic plaque, prevents its formation or even regresses its precursor fatty streak lesions? And if so, what are the implications for the prescription of exercise?

Physical Activity As A Mediator Of Endothelial Health

The apparent paradox, that acute exercise, though increasing the production of ROS, also chronically improves endothelial function, has long puzzled investigators [93]. Similarly fascinating is the observation that exercise training, in CVD patients, dramatically increases myocardial perfusion and lowers risk with no or little visible regression of coronary stenoses [94]. This gap between PA associated modification of risk factors and morphometric changes on one hand, and actual risk reduction on the other, has recently been termed the “risk factor gap”, which has become an area of intense research [95].

One obvious effect of exercise is a change in haemodynamics, generating flow patterns, which are substantially different from those of the resting state. That these flow patterns are causally correlated with endothelial function and, by extension, atherogenesis is a relatively new discovery.

Since the early Eighties it is known that plaque distribution is non-randomized with preferential development on the outer walls at arterial bifurcation points and downstream of existing plaques [96, 97]. The common denominator of these locations is a low shear stress experienced by the endothelial cells (ECs) [97, 98]. Shear stress is defined as the blood-flow’s frictional force acting on the cell surface in the direction of the vessel wall.

It has been shown that the promoter regions of the genes expressing VCAM and sICAM proteins contain elements, which respond to alterations in shear stress [99, 100].

Obviously, the EC’s mechanoreceptors respond to haemodynamic forces by initiating distinct molecular signaling cascades which either inhibit or promote inflammatory responses [101]. In the case of physiological shear stress, these cascades are anti-inflammatory and anti-adhesive, whereas the opposite is the case in areas of oscillating or low shear stresses [74]. Changes in haemodynamics, such as those resulting from exercise of appropriate intensity, can rescue the EC from unfavorable blood flow patterns. Mathematical modeling of abdominal aorta haemodynamics has demonstrated that the atherogenic blood flow patterns prevailing at arterial branch points under resting conditions can be eliminated by exercise [102].

Interestingly, a threshold seems to exist for exercise intensity, below which no beneficial change in EC response to exercise can be observed.

These observations, however, beg the question, how the relatively limited time spent in exercise of adequate intensity may possibly generate an effect on the vasculature that lasts long enough to be of atheroprotective significance.

Current evidence supports the notion of an indirect pathway via the activation of nitric oxide (NO) production, the bioavailability of which extends beyond the period of acute exercise. In contrast, a disturbed bioavailability of nitric oxide, formerly known as the endothelial derived relaxation factor (EDRF), promotes inflammation and thrombosis, thereby initiating and accelerating the formation of atherosclerotic plaque as well as its destabilization [103].

Further support for the notion of PA as a means to redress the SO/NO balance comes from animal and human studies. In wild-type mice, exercise training substantially increases NO as well as the expression of eNOS and ecSOD genes, leading to a net increase of NO compared to SO [104]. However, the same experiment with eNOS knockout mice, failed to increase NO, as expected, but also did not increase ecSOD expression, which suggests that NO is also a modulator of ecSOD gene expression, and hence the mediator of the anti-oxidant effects of exercise.

In CVD patients, 10-minute bouts of supervised exercise, performed 6 times daily on row and bicycle ergometers over 4 weeks, dramatically improved endothelial function, measured in-vivo and in-vitro [105]. In the exercise group, acetylcholine-mediated vasodilation and blood flow increased 2-fold and 8-fold respectively, whereas no change from baseline was evident in the sedentary control group. Also, eNOS-mRNA and eNOS protein concentration increased two-fold in the exercise group compared with the control group.

In middle-aged apparently healthy overweight and obese men, a 12 weeks exercise program significantly increased carotid artery compliance and plasma NO concentration [106].

An Interim Summary

Endothelial health depends on a finely tuned balance between pro- and anti-oxidative pathways. The disturbance of this balance has been appropriately termed endothelial dysfunction (ED) [107, 108]. It is the precursor of a pro-inflammatory state that promotes atherosclerotic vascular disease (AVD) and its endpoints. Hence ED is a primary target of interventions aimed at preventing AVD.

Endothelial cells respond to PA stimuli by maintaining or restoring the balance between pro- and anti-oxidative pathways, thereby maintaining or improving the anti-atherogenic vascular environment. Accumulating evidence supports the view that chronic intermittent exercise training improves endothelial function by increasing NO bioavailability [109] and that exercise is an effective atheroprotective therapy [109, 110].

Since there is compelling evidence for the strong and independent inverse association between PA and ED, increasing PA in sedentary at-risk populations is a promising strategy in the battle against AVD.

On a population level, however, this effectiveness is mitigated by low adherence rates to PA recommendations and interventions, a problem addressed in the following section.

The Behavioral Aspects: The Failure Of Free Will In Behavior Change

"In the mature sciences the prelude to much discovery and to all novel theory is not ignorance, but the recognition that something has gone wrong with existing knowledge and beliefs" Thomas S. Kuhn

It is an acknowledged fact that many people who are aware of the benefits of a healthy diet or of exercising regularly do not behave in accordance with their beliefs despite repeated resolutions to remedy this inconsistency.

The resolution to take up exercise is generally driven by (a) the awareness of its ultimate health benefits and (b) the anticipation that, at the planned point in time one will be motivated to choose exercise over a sedentary alternative. That however is self-contradictory. If one would innately prefer exercise to its sedentary alternative, one would not need a rational resolution. The very fact that one needs a rational resolution bespeaks an innate preference for remaining sedentary. This begs two questions:

First, why would one expect to prefer exercise over its unhealthy alternative in the future when one doesn't prefer it right now?

And second, if reason was the ultimate driver of our health behavior, why do we witness not only the anecdotal evaporation of new-year resolutions but also the stupendous degree of non-adherence to PA recommendations and interventions across interventions and populations?

Obviously, there exists some behavioral drive with the power to override reason and volition, the two mental-faculty champions of the volition-health camp.

But before presenting the evidence for the autonomous drive of physical and dietary behavior it is worthy to review the degree to which the belief in a rational control of health behavior is failing public health.

Non-Adherence To Physical Activity Recommendations – The Magnitude Of The Problem

Intervention effectiveness depends on the efficacy of the intervention and on the degree of adherence to it.

Despite several decades of public health messages about the benefits of physical activity, a majority of the population remains non-adherent to public recommendations and below the recommended levels of health enhancing physical activity (HEPA).

In a survey conducted in 2002 across EU countries, the percentage of sufficiently active adults averaged just 29% [14]. The guidelines used to define the threshold of health enhancing physical activity were drawn from the then valid CDC-ACSM recommendations (U.S. Centers for Disease Control and Prevention, and the American College of Sports Medicine) of accumulating at least 150 minutes of moderate-intensity exercise over 5 days per week or 60 minutes of vigorous-intensity exercise over 3 days per week [111].

In Germany 60% of the adult population falls below this threshold [14]. Whether these figures represent any improvement over the past decades is difficult to ascertain due to changes in measurement methodology and PA recommendations over the past 4-5 decades. An evaluation of the population of the Baltimore Longitudinal Study of Aging (BLSA) concludes, that public health recommendations had only a minor and transient impact on the prevalence of sedentism during the 70s and 80s and none thereafter [112]. However, with a 24% prevalence of sedentism in the 1960s and a 14% prevalence in the 1990s (all assuming the aforementioned CDC-ACSM guidelines) this self-enrolled and admittedly very health-conscious study population is hardly representative of the general population.

More telling are the effects of recent and current interventions. No reduction in morbidity or mortality was observed following a community-wide 5-6 year education intervention in the U.S., with only minimal improvements of risk factors [113]. In Germany, a similar 7-year intervention was conducted with the population of three large-city districts in Bremen, Berlin and Stuttgart, the entire medium-sized city of Karlsruhe (population ≈ 275,000) and two of its bordering communities, plus the rural district of Traunstein [114]. A statistically significant lowering of blood pressure by 2% (systolic and diastolic) was observed in the intervention vs. the reference population. However, given the large number of observations, statistical significance of this relatively minor change is unsurprising, and the clinical relevance of these results is questionable, as the study does not report on morbidity or mortality incidence. While the investigators observed a 21% reduction in untreated hypertension, this effect may well be due to an intervention-triggered sensitization of individuals, who subsequently sought medical attention, and who would otherwise have remained ignorant about their hypertensive state. It is also telling, that the prevalence of BMI >25 increased in the intervention population by 2% despite the targeted 5% reduction.

In the UK the ACTIVE for LIFE campaign, which aimed at promoting increases in physical activity, yielded no measurable behavioral change at a cost of £ 3’ Mio [115].

Again in the UK, physical activity referral schemes (PARSs) have become a widely used primary care tool to encourage sedentary adults to take up exercise [116]. PARSs generally

entail the referral of a primary care patient to a 10-12 weeks supervised exercise program [117]. Of the 75% of referred patients who took up the referral, 48% completed the program, with completion defined as having attended at least 80% of the prescribed exercise sessions [116]. This translates into only 36% of referred patients completing a physical activity program, which had been specifically prescribed by a primary care physician to reduce a diagnosed health risk.

Smaller-scale clinical and commercial interventions do not fare much better.
Dropout rates from physical activity programs are typically 50% within the first 6 months [118-120].
Taking weight loss in obese persons as an outcome measure of exercise and diet based weight reduction trials, an almost entire reversal of initially achieved weight loss is observed within 3-5 years post-intervention [121, 122]. When defining long-term weight-loss success as losing initially ≥ 10% of bodyweight and maintaining at least 10% bodyweight reduction at 12 months, the most optimistic estimates of success rates are 20% [123].

Amazingly, even with the agony load of having suffered a myocardial infarction, at 6 months post-infarction, 60% of patients have been found to be insufficiently physically active to lower the risk for a repeat event [124].

Using the internet as a tool to reach larger numbers of individuals does not seem to help much either. Active-online is a web-based, German-language, individually tailored physical activity program that had been developed by a group of experts drawn from various health sciences [125]. This program is directed at adults aged 30 to 60 years. In a 13-months follow up of 1,500 users, self-reported PA increased significantly, however, these data are in conflict with objectively measured PA, which showed no increase at all [125].

A Danish 20-weeks work-site PA program using pedometers and a 10,000-steps-a-day program goal resulted in no change of PA in the intervention and control groups [126]. To make things worse, those intervention group participants whose daily step count exceeded 10,000 steps at baseline demonstrated a statistically significant 13% drop in step counts at follow-up. No changes were observed among participants whose daily step-counts had remained below 10,000 steps at baseline, regardless of intervention or control group. While the drop in step-count may be explained by seasonal effects (follow-up was in February) the overall result does not give reason for enthusiasm.

The aforementioned intervention examples are an illustrative rather than an exhaustive list, which highlights the extent of the non-adherence issue. Non-adherence has become such a sizeable problem that the WHO has recognized it, in its 2003 action paper on adherence, to compromise the public health effectiveness, not only of lifestyle change interventions, but across all therapeutic areas [127]. The WHO also criticizes that adherence can’t be measured and compared across interventions as there are no specific adherence standards against which participant behavior can be compared. This is particularly problematic in physical activity interventions, where adherence has been variably defined as attendance at the final

session, or by variable percentages (generally 75% - 80%) of sessions attended, either on the participant or the group level [116]. Neither of these definitions reliably tells us whether the label “adherent” reflects (a) adherence throughout the intervention, or (b) stable change of PA behavior, the latter being the primary objective of public health efforts to increase PA levels.

Taken together, the discussed evidence supports the WHO view that non-adherence is such a substantial confounder of intervention effectiveness, that improvement of adherence is expected to have a larger impact on public health than advances in specific medical treatments [127]. That begs the question: What are we doing about it?

Non-Adherence to Physical Activity Recommendations – Current Strategies To Solve The Problem

Any discussion about adherence necessitates first a definition of the term. The WHO has defined adherence [127] as “*the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider.”*

The emphasis on the term “agreed” acknowledges the importance of the role of the patient as a consenting party to a therapeutic or preventive curriculum, and to differentiate adherence from compliance.

While adherence is a measurable behavior of the patient, its drivers do not exclusively rest with the patient. The WHO recognizes health care providers and health care systems as important contributors to adherence behavior [127]. I will briefly summarize the role of these external drivers of adherence before discussing its behavioral aspects in greater detail.

The Public Health Strategies

Health care providers’ communication skills, from history taking to discussing the therapeutic intervention, have been found to somewhat correlate with functional and physiological outcome [128]. However, this statement needs to be viewed in the context of a lack of standardized instruments to reliably evaluate doctor-patient communication and relatively little published data on this subject [129].

A Cochrane review of clinical trials showed inconclusive evidence that simply counseling adults in the primary care setting is effective in increasing physical activity [130]. However, common sense suggests, that a well-informed patient, whose doctor treats her as a partner in the treatment process, will be a patient more willing to adhere to the treatment program.

As long-term adherence to changed behavior is required to maintain its benefits, relapse prevention is essential but, again, requires provider follow-up. At which intensity such encouragement needs to be delivered is less clear [131].

The American Heart Association (AHA) exhorts physicians to provide their patients with this encouragement in the form of individualized exercise prescriptions and familiarization with

behavioral change strategies [38]. But expecting health care providers to follow this call, without the health care system providing the necessary incentives, appears naïve. A recent survey of primary care physicians confirms this view [132].

After all, it is the health care system which directs (a) duration and frequency of doctor-patient interaction, (b) efforts for maintenance of care, and (c) the financial reimbursements. These directions have evolved from a need to treat acute disease, not from a need to prevent the chronic variety. Inevitably, with resources already stretched to meet the demands for acute care, current health care systems would be overwhelmed by the demand for preventive services. The WHO has therefore recognized these systems as falling “remarkably short” when tasked with preventing and managing chronic diseases [133].

The good news is that the WHO has acknowledged the need to move towards an integrated preventive health care system, but also, that this requires nothing less than a paradigm shift [133]. The bad news is the glacial pace at which such restructuring happens.

However, every problem also presents an opportunity. The opportunity in this case is for a tool that allows (a) a cost-efficient dissemination of variably designed PA interventions across large populations, that (b) provides for standardization of adherence and outcome measurement across interventions, and which (c) increases the prevalence of health enhancing physical activity. Before conceptualizing such a tool, it is necessary to review the behavioral mechanisms underlying PA habits.

The Strategies Of Behavioral Science

While extensive efforts have been made to identify personality traits that help predict adherence, there is no evidence of adherence being associated with any specific trait [127, 134]. Equally futile has been the search for a behavioral model, which would not only explain patient behavior but also facilitate its modification to promote adherence. These efforts have produced an array of models and theories, which I will briefly summarize on their key aspects as these relate to the acquisition of HEPA habits. One conclusion that can be safely drawn from this proliferation of models is, that obviously nobody has uncovered the heart of the matter.

Therefore I antedate this discussion with its essential result that, while all these models have their advantages and deficiencies, none has proved to be superior, and a call for their integration into one combined approach has been made [135].

The Health Belief Model (HBM)

The HBM [136] posits that an individual will make a health behavior change if she/he believes that:

- negative health consequences can be avoided
- the recommended behavior change prevents the feared health consequences
- she/he has the ability and resources to carry out the recommended behavior change

The HBM is built on four constructs representing an individual's perception of susceptibility to the disease, severity of the disease, benefits of preventing it and barriers to the recommended behavior change. Taken together, these four constructs determine an individual's readiness to act, which requires a cue to action to set the behavior change in progress.

A 1992 meta-analysis of the HBM found it to have been, until then, the most frequently cited model in health research [137]. However, the authors also reported inconclusive evidence to recommend for or against the usefulness of the model. As none of the underlying studies was concerned with HEPA as the dependent variable and only one with dietary behavior in obesity, the usefulness of the model as a framework to guide PA intervention protocols remains uncertain. Since the aforementioned meta-analysis, several cross-sectional studies have reported on the usefulness of HBM constructs to predict exercise behavior in college women for the prevention of osteoporosis [138, 139], in type-1 diabetic college students for the prevention of complications [140], and in type-2 diabetes mellitus (T2DM) amputees [141].

In a retrospective study of 69 clients of a community centered 6-months CVD exercise program, HBM constructs had shown only modest association, no association and a counter-intuitive association with exercise behavior [142]. However, this study had serious weaknesses such as the facts that all subjects were attendees of an exercise program and that health belief questions had been answered retrospectively after conclusion of the program. Overall, published data on the utility of the HBM for PA interventions are sparse, all studies are cross-sectional and hence no data are available to answer the question whether a change in the HBM constructs yields a change in exercise behavior in the expected direction.

The Theory Of Reasoned Action (TRA)

The focus of TRA is on an individual's attitudes towards the outcome of a behavior as the major determinant of the intent to carry out the behavior [143, 144]. As such, TRA applies best to behaviors, which are entirely under volitional control. That assumption does not necessarily apply to lifestyle behaviors, specifically the acquisition of HEPA, which are also influenced by factors outside of an individual's purely volitional control, as discussed in the next section. To accommodate for this fact, TRA has been refined into the Theory of Planned Behavior.

The Theory Of Planned Behavior (TPB)

The theory of planned behavior (TPB) is an extension of TRA [143]. It acknowledges the importance of assessing the amount of control an individual has over the target behavior. Control factors relevant to HEPA are internal factors, such as skills, abilities, information and emotions, as well as external environmental factors.

The Transtheoretical Model Of Behavioral Change (TTM)

The transtheoretical model of intentional behavior change describes the process of behavior change as evolving through 5 distinct stages: pre-contemplation (not ready to take action); contemplation (getting ready); preparation (ready); action (overt change) and maintenance (sustained change) [145]. In each stage specific *processes of change* are required to facilitate the move to the next stage. Recidivism to an earlier stage is always possible and individuals may cycle through these stages several times before a stable habit keeps them in the maintenance stage. The model also incorporates a series of intervening or outcome variables, such as *decisional balance* (the pros and cons of change) and *self-efficacy* (the perceived ability to perform a task).

A 2008 systematic review investigated 21 randomized controlled trials and 3 non-randomized controlled trials, all conducted between 1996 and 2005, which had applied TTM to develop PA behavior change interventions under the hypotheses that these interventions are effective in promoting PA behavior [146]. The authors report that only 7 interventions were tailored to all four dimensions of TTM (specifically stages of change, processes of change, decisional balance and self-efficacy). However, all of these reported statistically significant short-term findings, and 1 intervention statistically significant long-term findings. Since also 12 of the remaining 17 interventions reported significant short-term findings, the reviewers felt unable to conclude whether studies, which do not deploy all TTM constructs are any less efficient than ‘full-model’ interventions. Particularly relevant to HEPA as the outcome measure is, that only one of the reviewed trials reported on statistically significant long-term findings over 12 months.

One study, not included in the aforementioned review, conducted with Chinese adolescents found only weak correlation of the TTM to predict exercise behavior [147].

The Social Cognitive Theory (SCT)

Perceived efficacy is the key determinant of social cognitive theory [148]. This theory suggests, that the stronger the perceived efficacy in changing lifestyles, the higher the goals the people set for themselves, and the greater their trust in their ability to overcome obstacles to achieve the desired outcome. In this model, a patient’s adherence to lifestyle change depends largely on his self-regulatory skills, which includes self-monitoring and self-management. There is some evidence to suggest that constructs of social cognitive theory

associate moderately with uptake of HEPA in diseased [149, 150] and healthy [151, 152] populations.

A proactive approach by the provider necessitates imparting the requisite physical activity and lifestyle change skills as much as instilling the patient's belief in having them.

The Protection Motivation Theory (PMT)

The Protection Motivation Theory is built on four constructs, which are thought to underlie an individual's decision how to deal with a potential health threat. These four constructs are:

1) The perceived *severity* of a disease outcome (e.g., a heart attack)
2) The perceived *vulnerability* (the probability to suffer a heart attack)
3) The perceived *response efficacy* (the efficacy of the recommended preventive action)
4) The perceived *self-efficacy* (the degree of confidence in one's ability to perform the preventive action).

Protection motivation is the result of the threat appraisal (constructs 1 & 2) and the coping appraisal (constructs 3 & 4). In the context of HEPA protection motivation refers to the intention to take up exercise and to maintain it for preventive purposes. To judge the usefulness of this model for promoting the uptake of HEPA is difficult as there are insufficient studies available to draw any conclusion.

The Health Action Process Approach (HAPA)

HAPA is based on the staging of health behavior, and consequently health behavior change, from pre-intentional motivation processes which generate behavioral intention, to post-intentional volition processes which promote the actual health behavior [153].

In the motivation phase the constructs of self-efficacy and outcome expectancies are seen as the most relevant predictors of intentions. In the volition phase the perception of self-efficiency becomes the determining element as action plans and their realization depend largely on one's perceived competence to execute them.

A General Criticism Of the Models

What is striking in these models is not their diversity but their common denominator: the elements of reason, perception and volition.

Common to all models is the implicit assumption of volition as the final authority determining an individual's behavior, while all other model-specific determinants affect the likelihood of this behavior to happen in the predicted direction. Discrepancies between observed and predicted behavior may consequently be ascribed either to the inadequacy of a model's

constructs to predict behavior, or, in a less benevolent view, to an inadequacy of volition, or more colloquially, lack of willpower.

> The beauty of the latter view is that it enables public health actors to place the responsibility for the consequences of detrimental health behaviors squarely on the "aberrant" patient. Aside from other nuisances, this relieves the health care actor from inconvenient confrontations with industries who derive their economical successes from tempting people into unhealthy patterns of consumption and behavior, thereby contributing substantially to the health care actors' taxation revenues.

In the following I will present evidence, which is irreconcilable with the view of health behaviors being driven by reason and volition.

The Reason For Non-Adherence: Evidence For The Failure Of Free Will

Health Behavior In Children

Children are too young to choose being overweight or obese. But if the volition-health assumption were true, children would be able to change once the agony load from being overweight crosses a threshold that motivates them to replace obesogenic behaviors with healthier alternatives.

The bodyweight related agony load is indeed high for obese children. They suffer not only in terms of poor health related quality of life (QoL), which has been found to be equivalent to that of child cancer patients receiving chemotherapy [154], but also in terms of peer victimization and stigmatization [155]. Yet, the prevalence of overweight among U.S. children and adolescents has nearly tripled over the past thirty years from 5% in 1971 to 13.9% in 2004 [156]. The steepest increase was in the bracket of 6-11 year-olds in which overweight prevalence climbed from 4% to almost 19%.

Today these kids face substantially more stigmatization and negative stereotyping than obese children did 40 years ago. In a 2003 replication [157] of a 1967s experiment [158] 458 5^{th} and 6^{th} graders were asked to rank their liking for (a) a healthy child, (b) one with clutches and a leg brace, (c) one without a left hand, (d) one sitting in a wheel chair, (e) one with a facial disfigurement and (f) one obese child. In both experiments the kids ranked the healthy child highest and the obese lowest. The bias against the obese child, though, had increased by over 40% in the 40 years that separated the two experiments. Interestingly, while boys and girls agreed on a strong dislike for the overweight child, boys had a clear preference for functional ability whereas girls for physical appearance. This anti-obesity bias translates into overt and relational peer victimization, from which overweight youths suffer more than normal-weight children [159].

It is therefore not surprising that low self-esteem is more prevalent in overweight children, specifically those who self-attribute their weight status [160]. The dislike for a fat physique is

so prevalent that 50% of 2nd – 6th graders express dissatisfaction with their body weight and 16% report past or present attempts at weight loss [161].

Despite all the suffering and all the remedial efforts, behavioral change programs for weight reduction in obese children and adolescents have remained remarkably inefficient. While improvements in knowledge and self-reported health behaviors are tangible, effects on BMI are not [162].

If obesity was a result of behavior and behavior a matter of choice then the volition-health camp owes us an answer to the question why children and adolescents choose to be ostracized, victimized and to suffer from low QoL.

Health Behavior in Adults

Discrimination and mistreatment continue into the adult years of the obese person [163]. The disadvantages of being obese are most tangible in the areas of health care, employment, and social life. One in 4 nurses reports being repulsed by obese patients [164]. The percentages of biased health care professionals may vary depending on study design, but a generally more negative attitude of nurses towards the obese patient is apparent across studies [165].

The obese person pays a substantial penalty on wages, at least in the first two decades of professional life [166]. Obese persons are also less likely to find a sex partner, with men showing a strong selection bias against overweight/obese females [167]. The stereotyping and stigmatizing even pervades the very professionals, who deal with preventing and reversing obesity. Exercise science students show a strong bias against obese people, again equating obesity with laziness and bad attitude [168].

Ironically, diet advertisements reinforce the stigmatization and stereotyping of the overweight/obese individual. The frequently used before-after portraits of weight-reduced individuals appear to strengthen the belief that weightloss is a matter of volition and effort, thereby reinforcing the stereotyping of obese individuals as lazy [169]. This stigmatization is so pervasive, that even obese people themselves endorse the stereotypical fat-lazy equation [170].

If the volition-health assumption was true, then, with the prospect of a substantial increase in QoL added to the well-known health benefits, obese people should be particularly motivated to adhere to PA interventions. The evidence says otherwise. In a community-based program of behavioral change for overweight and obese persons 53% of participants had dropped out within the first 6 months [120]. This is a particularly telling figure, given the vested interest of the participants, who had to pay a US$ 350.- enrollment and orientation fee plus a US$ 135.- monthly retainer. Unsurprisingly, participants had an above-average socio-economic background with over two thirds being college graduates and more than half having an annual

income in excess of US$ 60,000.-. That is not exactly the profile that fits the supposedly weak-willed, uneducated and unaware person.

Confronted with this ubiquitous behavior, which does not reconcile with the view of humans as a rationally acting species, impulsivity has emerged as a more palatable term in efforts to keep volition and reason the champions of health behavior.

Impulsivity And Behavioral Economics

Irrational health behavior can be described as impulsively choosing an immediate smaller reward (e.g. pleasure of remaining sedentary) over a larger but later reward (health benefit, QoL), despite having previously expressed a preference for the latter.

Behavioral economists have been puzzled by a very similar phenomenon.
When given a choice between a larger later payoff and a sooner smaller payoff, people generally express a preference for the larger payoff, if both payoffs are reasonably distant in time from the time of making the choice [171]. However, given the choice between the same payoffs and the same time lag between these payoffs, but with the smaller payoff being offered immediately, people generally opt for the smaller payoff. To illustrate this behavior in a hypothetical experiment, given the choice of receiving €100,- in 5 months or € 120,- in 6 months, most individuals will choose the 6-months €120,- option. However, if given the choice between receiving €100,- right now or € 120,- in one month, the same individuals will prefer the immediate payoff of €100,-. Since both inter-payoff periods and both amount options are the same, individuals' choices are obviously not based on constant-rate discounting, which would compel them to consistently choose one option over the other regardless of the time-lag between decision and pay-out. When attempting to express these empirical data mathematically, hyperbolic functions emerged as the best fit [172].

Impulsive Discounting – An Attempt to Explain Irrational Behavior with Rational Tools

From these observations Ainslie [173] developed the discounting model of impulsiveness. At its core is the theory of "hyperbolic discounting" of rewards which pitches a larger-later reward (e.g. good health) against a smaller-sooner reward (e.g. gratification from a sedentary activity) in hyperbolic discounting curves (Figure 1).

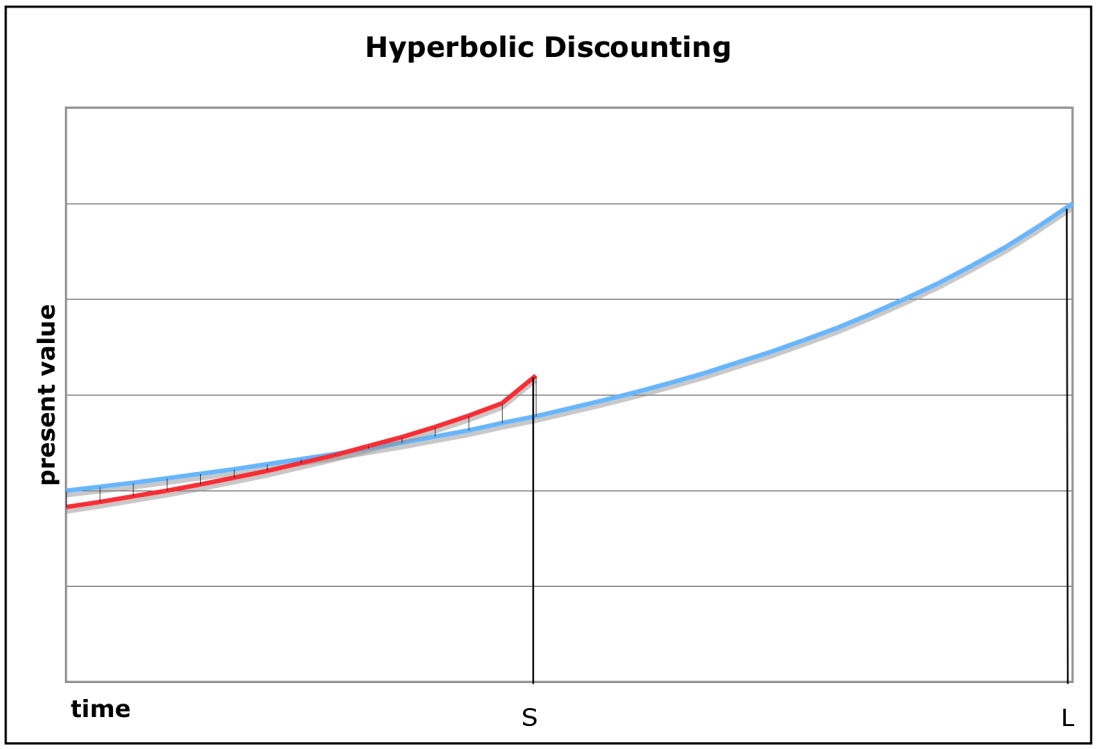

Figure 1. **Hyperbolic Discounting**

An individual might find himself in this situation after having made the new-year resolution of taking up health promoting exercise after the holidays. Hyperbolic discounting predicts that this individual will likely switch reward preference from health benefit to sedentary bliss when the latter is up for immediate consumption, as at that time he will have passed the cross-over point of the two discounting curves.

While the model of impulsive discounting nicely matches empirical and experimental evidence in humans and animals [171, 174-177], given the current level of understanding, I consider it to be of descriptive rather than explanatory value, and hence of little practical use in the arena of health behavior modification. For two reasons:

First, there is the problem of determining reward values and discounting rates. Even in experiments with monetary rewards, where the determination of reward value is relatively straight forward, there appear inconsistencies and changes across age and income groups [178]. It is easy to see how this problem may be compounded by the need to assign values and discount rates to immaterial rewards.

Secondly, while hyperbolic discounting is a useful description of the choices people make, the direction of a causal relationship, if any, between hyperbolic discounting and behavior remains uncertain [172]. In other words, does the phenomenon of hyperbolic discounting precede people's methods of making impulsive choices, or is it a chance mathematical observation that emerges as a consequence of some other underlying process which compels people to make choices in ways that are simply inconsistent with other discounting methods. The jury is still out on this question.

Recall that I began this discussion with the intent to challenge the prevailing belief in reason and free will as the drivers of human health-related behavior. While Ainslee's model neatly describes frequently observed and seemingly irrational behavior, it does not dethrone volition and reason as its ultimate ruler. Evidence emerging from addiction research, however, does, which is ironical, since it is addictive behavior, to which Ainslie's model is a near perfect fit.

Addiction – A Keyhole View to Neurohormonal Behavioral Drives

One does not need to elaborate the fact that addicts consistently choose the smaller reward of drug consumption over the larger and definite reward of not ruining their lives and their wellbeing. The urge to choose the drug reward is known to overpower even intense desires to kick the habit. Robinson and Berridge have dissected the neurohormonal underpinnings of this behavior into a model that not only reconciles with 'hyperbolic discounting', but from which we can also generate a strategy for health behavior modification [179].

In a theory, which originated from an attempt to explain the idiosyncrasies of addictive behavior, Robinson and Berridge implicated dopamine as the core neural substance that drives the "wanting" of the hedonic experience, which an organism has learned to associate with a certain drug [179]. What differentiates this Incentive Sensitization Theory (IST) from other addiction theories is the distinction of the "wanting" from the "liking" elements of addiction. The authors provide unequivocal evidence for each element to be associated with a separate neural architecture and neural substance. Briefly, the core elements of IST are the following:

(a) *Dopamine:* enhanced dopamine transmission is the common effect of addictive substances.

(b) *Incentive salience:* Dopamine's psychological function is the attribution of incentive salience to stimuli which the addict has learned to associate with the hedonic experience of drug taking, i.e. dopamine increases the "wanting" of the drug independently of the "liking"

(c) *Hypersensitization:* Repeated activation of the dopaminergic system, as a consequence of repeated drug taking, leads to the system's long-term, and possibly permanent hypersensitization, thereby increasing incentive salience

(d) *"Wanting" - "Liking" Dichotomy:* sensitization of the dopaminergic system is independent of the drug's hedonic effect, thereby driving a persistent drug craving and consumption despite unchanged or even diminished hedonic pleasures and greatly increased negative consequences to health and wellbeing.

It is particularly the last point, which unveils a striking similarity between drug addiction and dietary behaviors: Persistence of a detrimental habit despite awareness of its consequences, and habit relapse despite temporary habit change.

Within the IST paradigm, the difference between a heroin addict and a compulsive chocolate eater is merely the substance of choice not the habit's underlying physiology.

This similarity has not been lost on the theory's authors who support its applicability to feeding behaviors [180].

The Dopaminergic System And Feeding Behavior

The targets of food cravings are generally the sweet & fatty [181] and, to some extent, the salty varieties. Their power to generate hedonic pleasure is evident in the unconditioned facial responses of newborns demonstrating an innate preference for sweet foods [182]. This preference is shared by other primates such as chimpanzees [183], which suggests some evolutionary advantage for this preference. The pre-industrialized, pre-agricultural environment is characterized by an absence of processed food. Of the non-processed foods sweet-taste sensations are primarily evoked by fruits and other carbohydrate-rich foods, which are also rich in essential micronutrients and anti-oxidants [184]. An organism's innate hedonic drive to consume these foods would have ensured it's seeking them out to repeat the pleasurable experience. Similar mechanisms may reasonably be suspected behind the human preference for foods with fatty texture, which signals high energy content. On the other hand, an innate dislike for bitter tastes has obvious protective functions against the consumption of plants containing potentially poisonous, bitter tasting alkaloids.

And so it is conceivable that the dopaminergic system, being effective in driving an organism to the food, which ensures survival, evolved as a consequence of natural selection.

That mechanism however has become maladaptive in the context of today's food environment, which can summarily be described with the adjectives "aplenty", "available" and "energy dense", with high concentrations in sugar and fat.

Their "dopaminergic appeal" fuels a human "wanting" of these foods with an intensity that frustrates conscious attempts to replace them with healthier but less stimulating alternatives.

The addictive power of sweet tastes has been demonstrated in mice, genetically altered to reduce synaptic dopamine clearance by 90%, exposing the rodents to a persistently higher dopamine level than wild-type mice. In these mutants the "wanting" of a sweet reinforcer was substantially greater despite no elevation in the "liking" of a sweet reward [185].

There is also considerable evidence to show that sucrose feeding can activate the dopaminergic system in a dependency producing manner [186, 187].

A more recent experiment demonstrated that nucleus accumbens corticotropin releasing factor, which initiates the stress-triggered cascade of hormones of the hypothalamus-pituitary-adrenal axis (HPA-axis), amplifies dopaminergic incentive salience [188]. This may explain the observation that chronic stress leads to increased food consumption thereby promoting obesity [189].

It has also been observed that under conditions of classical conditioning, in which a hitherto unrelated stimulus is paired with food presentation, food intake increases when hunger and the now conditioned cue are paired subsequently [190]. It is easy to see the relevance of this phenomenon, which has been termed conditioned potentiation of feeding, to human feeding behavior. Once stimuli, such as time of day, physical location or presence of friends have been conditioned into cues for food intake, dopaminergic drives to eat in excess of physiological need are aroused. The obvious consequence is overweight and obesity and a conditioned resistance against rational attempts at reversing this situation through health behavior change.

These observations have finally begun to be recognized by practicing physicians as evidenced in the recent discussion of neuroendocrine drives of obesogenic behavior and its striking similarity with addiction [191]. Still, the belief in reason as the desired driver of health behavior shines through in the author's implied endorsement of current considerations to classify obesity as a psychological disorder. With this I disagree. If obesogenic behavior is driven by evolutionary conditioned neurohormonal mechanisms, it is not a psychological disorder. Rather is it the temptations of the modern environment to which these mechanisms are maladapted. With respect to health behavior, these mechanisms are the genie in the bottle. From within its bottle, this genie has served humans well throughout evolution. But the profound environmental changes of the past 50-100 years have released the genie, which now wracks havoc with our health. How difficult it is to tame through pharmacological means becomes evident in the very moderate success of the first pharmacological anti-obesity agent, which directly manipulates the homeostatic hypothalamic drive, Sibutramine [192], and the near disastrous consequences of another modulator of feeding behavior, Rimonabant, a cannabinoid receptor antagonist, which has been withdrawn from EU markets barely two years after its introduction.

A New Model For Physical Activity Behavior – Accounting For Its Neurohormonal Underpinnings

Does the dopaminergic system play a role in physical activity behavior? Probably not. The purpose of briefly diverting the discussion into the arena of obesogenic feeding behavior was to illustrate, that neurohormonal states are very powerful drivers of health behavior, virtually unopposed by reason and volition.

PA behavior is distinct from feeding behavior in that there is no conceivable dopaminergic attachment to sedentism.

However, PA is also driven by neurohormonal states, which are tightly interconnected with feeding behavior. The evidence in support of this originates from an array of animal and human studies into the effects of the two neuropeptides, which have emerged as major orexigenic and anorexigenic players: neuropeptide Y (NPY) and leptin. To understand the intricacies of their antagonistic interaction, we need to first dissect human feeding behavior into two distinct activities: appetitive ingestive behavior (AIB) and consummatory ingestive behavior (CIB). AIB is all activity related to foraging and hoarding of food, whereas CIB is the act of feeding. This distinction is 90 years old and had, to the best of my knowledge, first been documented by Wallace Craig in his 1917 publication about the feeding behavior of doves [193]. It is immensely important when dissecting the orexigenic effects of NPY, which had first been sequenced in 1982 [194], and which has subsequently been found to be the only true, and very potent, appetite signaling molecule in the brain currently known to science [195]. Until then, most studies on the effects of NPY on rodent feeding behavior did not differentiate between the two behavioral components – AIB and CIB. More recent investigations, however, have facilitated a more detailed view about the effects of NPY and leptin on AIB and CIB.

To summarize the current body of knowledge as it is relevant for this discussion: NPY is produced in the brainstem and the hypothalamus. Its expression is regulated by various neuronal and hormonal pathways, such as the circadian clock, insulin and leptin, and glucocorticoids [195]. Conversely, leptin is chiefly produced by fat cells in proportion to their fat content. Its production follows a circadian pattern, with a low during the inactive period and rising to a high during the active period of the day. As this pattern coincides with the circadian pattern of feeding and fasting, leptin is currently assumed to be a hormonal transmitter, which, in an anticipatory fashion, signals to the brain to reduce and eventually terminate the drive to eat [195]. Without distinguishing feeding behavior into its two components, NPY is an orexigenic peptide, stimulating food intake, whereas leptin has the opposite effect. However, this view turns out to be too simplistic, as both hormones exert distinct and opposing effects on the AIB and CIB components of feeding behavior. Elegant experiments with rodents have demonstrated, that NPY exerts its orexigenic effect by powerfully driving foraging behavior, while weakly inhibiting CIB, whereas leptin administration strongly reduces the drive to forage but increases consummatory behavior [196]. That is, NPY drives the organism to “move to eat” whereas leptin opposes this effect.

The complexity of the interaction between the orexigenic and anorexigenic pathways of NPY and leptin is beyond the scope of this dissertation. Hence I attempt to summarize this interaction as it is relevant to the search for a working model of human health behavior, specifically that of physical activity and dietary behavior. It could be said that leptin represents an energy status signal. Its absolute concentration informs the brain about the level of energy reserves, and through its stable circadian fluctuation, it establishes a feeding pattern. Conversely, the rise and fall of brain-derived NPY concentrations reflects the current direction of energy flux. That is, diminishing energy reserves initiate appetitive ingestive behaviors with the goal of reserve restoration, the strength of this drive being somewhat modulated by reserve size. The latter is encoded in the strength of the leptin signal. This feedback loop inextricably integrates the organism to its environment in which the PA cost of food and its energy density represent environmental effector signals which modulate the behavioral response of the organism. In this model of homeostatic control the behavior of the organism is the target of feedback control. This does not reconcile with currently favored biomedical models, which are based on the assumption that body weight is the target of an autonomously operating homeostatic control, as suggested by set-point theory [197]. The latter model however, runs into problems with the observations of a steadily increasing bodyweight cross-sectionally in our society, and in most individuals longitudinally. Both observations violate the theory's prediction of weight stability.

In an attempt to reconcile theory with observation, the failure of this system has been blamed on a "purely cognitive/executive decision"-override of homeostatic body weight control [198].

Contrary to this view, the proposed new model, in which behavior, rather than bodyweight, is the homeostatically controlled parameter, does not require reason and volition as a convenient scapegoat. It resolves this issue on three levels:

***First*, the evolutionary point of view:** It is easy to see how distinct behavioral patterns, which enable an individual to overcome the supply challenges of a variable environment, carry a survival value. A strong drive to forage when energy supplies dwindle has a definite survival value. It is probably therefore that the NPY system is active in all vertebrates and even in some fish [199, 200].

In contrast, an ability to cap body weight would have increased inclusive fitness only if environmental conditions had facilitated pathological weight increase to the point of affecting an individual's chances to reproduce and survive. This is hardly reconcilable with our current understanding of the scarcity, fluctuation and unpredictability of food supplies that has characterized the environment throughout evolution.

***Second*, resolution of the prediction-observation mismatch:** Figure 2a is an illustration of the proposed model as it would be operant under the environmental conditions, which prevailed during formation of the human genome.

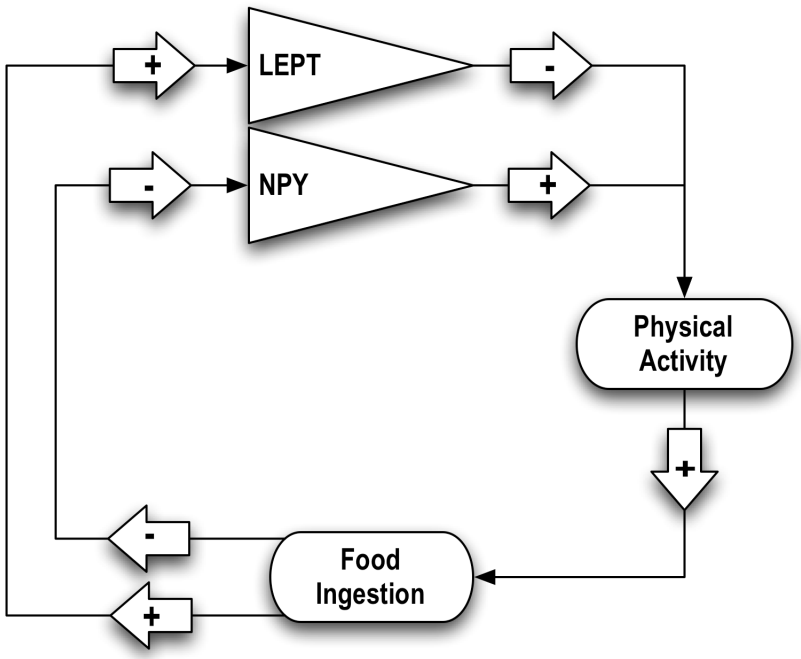

Figure 2a. **Negative Feedback Loop Of Energy Homeostasis**

In this model leptin and NPY represent the signals received by the loop's receptors, which inform the control center (brain) about the current reserves and flux of energy. The control center initiates the adequate behavioral response, which consists of an obligatory PA behavior as its appetitive component, followed by the ingestive component. This behavioral response will vary with the cost of food and its energy density, thereby maintaining homeostasis within a range of environmental conditions. The system will only fail when the food ingested in CIB is insufficient to replenish the energy expended for its acquisition. In other words, if the cost of food exceeds the organism's "capital" over a sufficient number of cycle revolutions, the depletion of capital will result in death. In rodent experiments, limiting food access to below a certain time threshold causes some animals to reduce food intake to below what the organism requires to compensate for the excess energy expended during NPY driven hyperactivity (increase in AIB), even if a sufficient amount of food is being made available during the access time [201, 202]. A similar phenomenon has been observed in human starvation and in anorexia nervosa [22].

How this system fails in our contemporary affluent society is shown in Figure 2b.

The only difference to the situation in Figure 2a is the removal of the obligatory AIB component, which exposes the CIB component directly to the receptor signals leptin and NPY, and their stimulating and inhibiting effects respectively, as these have been

demonstrated in laboratory animals [196]. Feeding in excess of energy need is pre-programmed in this loop, as the energy-status signal leptin more strongly stimulates CIB than NPY attenuates it.

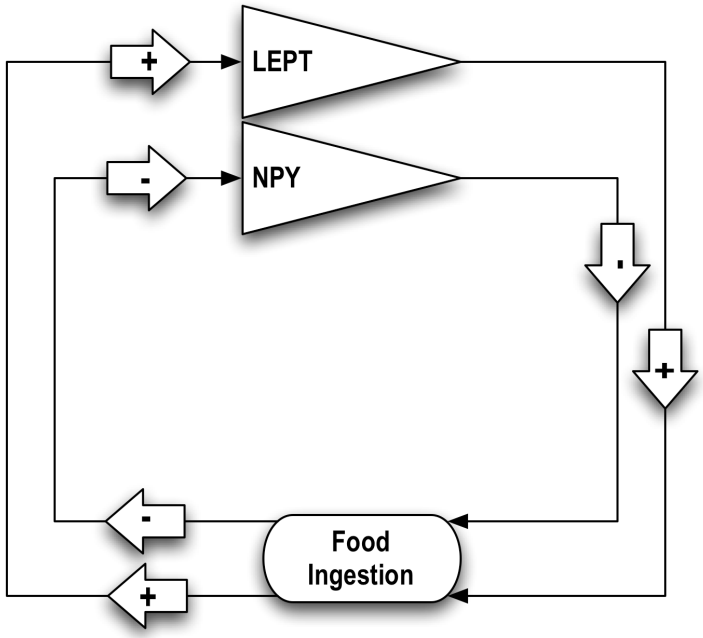

Figure 2b: **Disturbed Feedback Loop w/o Physical Activity**

Indirect support for this view comes from studies on the association between leptin and weight change in obese individuals who attempt to lose weight. It has been shown that the leptin/BMI ratio is a very strong predictor of weight loss success with an inverse relationship between baseline leptin/BMI ratio and weight loss at follow up [203]. The rate at which the inevitable weight gain will happen is determined solely by the net effect of the balance between the strength of the drive to eat, the energy density of the self-selected food and the energy expended through some independently (and voluntarily) performed PA.

Third**, resolution of the cognition-behavior gap:** the proposed model does not require a cognitive element, neither in its intact configuration (Figure 2a) to explain self-starvation, nor in the incapacitated configuration (Figure 2b) as the culprit driver of eating in excess of need. Excess food consumption is the naturally occurring consequence of a homeostatic loop in which its effector (PA) has been knocked out. Cognition may enter this model as the potential rescuer, reestablishing weight homeostasis through the introduction of voluntarily performed exercise as a means of energy expenditure. Indirect evidence in support of this concept comes from several investigations.

In a prospective 5-year survey of almost 10,000 Swedish individuals, BMI increase was absent only in the group of respondents who reported having implemented an exercise routine since baseline assessment [204]. BMI increase was lowest in the group who reported being physically active at baseline and at follow-up. Significant weight gain affected all other groups across age and BMI.

The U.S. National Weight Control Registry (NWCR) maintains the records of exceptionally successful “losers” with an average weight loss of 33 kg maintained over at least 5 years [123]. Entry requirements into the NWCR are a minimum weight loss of at least 30 pounds maintained over at least 12 months (http://www.nwcr.ws/).

A 1-hr daily exercise regimen has been found to be a key criterion behind this success [205], together with a behavioral strategy of self-monitoring of weight [206].

If neurohormonal pathways are the drivers of exercise behavior, this effect is heritable and should be confirmed in genetic linkage studies. In fact it is. A study of 37,000 complete Caucasian twin pairs from 7 countries (Australia, Denmark, Finland, Netherlands, Norway, Sweden and the U.K.) showed a heritability ranging from 27% to 71% with a median of 62 % [207]. In Pima Indians, a native American population with a high prevalence of diabetes, a specific polymorphism of the gene encoding the leptin receptor has been found to be associated with 24-hr energy expenditure [208]. This specific polymorphism is thought to decrease the receptors’ binding capacity for leptin, which, in this investigation was linked to lower 24-hr energy expenditure measured in a respiratory chamber. While this does not explain any potential effect on “voluntary” exercise-based energy expenditure, it shows that energy metabolism is genetically linked to the very same hormone, which is an instrumental effector in the above proposed model. In a genome-wide association study of 2,700 U.S. and Dutch adults, that particular polymorphism showed a marginal association with PA behavior, the latter being additionally and more strongly associated with polymorphisms in two intergenic regions [209]. The small size of the effect is potentially due to the limited number of study subjects, which gives the study a low power to detect small effect sizes, with the latter being expected in a behavior, which is very likely associated with multiple genetic drivers.

What I hope to have made obvious in this discussion is the pivotal role of PA behavior, not only for the prevention of CVD, as I have argued in the introductory section, but also as the effector of a controlled feedback loop for maintaining human energy homeostasis within an environment that places an energy cost before energy supply. The essential difference between this proposed model and the current biomedical view is (a) the differentiation of feeding behavior into its appetitive and consummatory aspects, and (b) the replacement of body weight with energy status and energy flux. The latter also makes intuitive sense. While there are hormonal and neuronal signals, which provide the brain with information about energy reserves and energy flux, we obviously have no sensors for body weight *per se*.

While inter-individual variability exists for the association between bodyweight and disease risk, continuous body weight gain is a strong indicator for the hypokinetic lifestyle, which presages CVD, and which is the hallmark of an environment from which the autonomously controlled PA cost of food has been eliminated.

In this environment the PA behavior, which is necessary to reestablish weight balance, is not part of any autonomously operating human homeostatic feedback loop. It therefore depends on cognitive supervision and control. That is, for PA behavior to be effective and sustained, the implementation of a feedback loop is required, with a cognitive receptor and control function to continuously match the effector PA behavior with rationally determined health goals.

Unless an intervention succeeds in:

(a) modulating the effector PA to the point where it re-establishes energy balance and

(b) maintaining the individual in this situation,

the intervention will fail, and the individual's eventual reversion to pre-intervention weight and sedentary status is inevitable.

The implications of these observations for the objective of improving adherence are obvious. It requires the:

(a) definition of behavioral goals in agreement with the individual's health profile, her preferences, abilities and environmental demands,

(b) definition of measurable behavioral goals to facilitate a comparison of actual progress vs. goal achievement

(c) periodic re-adjustment of the behavioral goals to optimize outcome and to accommodate changes in health and other profile parameters.

For convenience, I will use the terms individualization, self-monitoring and continuity to refer to these three demands in the above sequence.

The concluding part of this section will discuss the rationale behind these three aspects and the evidence supporting it. The section will conclude with a hypothesis for testing a tool designed to enable researchers and clinicians to translate the model into practice.

METHODS: TRANSLATING THE NEW MODEL INTO BEHAVIOR CHANGE PRACTICE

THE THREE ESSENTIAL ELEMENTS

Individualization

General Considerations

The one-size-fits-all approach of public health efforts has been criticized as a major cause of the failure to produce lasting health behavior change in the population [15].

This, however, is not necessarily due to public health actors' neglect of or disregard for interindividual differences within target populations, as has been suggested [15]. Rather is it the methodology of the research from which our knowledge about the health enhancing effects of PA has emerged.

The evaluation of randomized controlled clinical trials is based on intention-to-treat analyses, which depend on standardized group-specific protocols and predetermined dependent parameters, both applicable across all participants, to assess and measure intervention effects. But standardized intervention protocols likely conflict to varying degrees with participants' idiosyncrasies of expectations, abilities, preferences and the environmental demands imposed on them. The greater this conflict, the more likely is a participant's drop-out or post-interventional discontinuation.

In comparison to our knowledge about the health effects of changed physical activity behaviors, we know very little about how the disparity between intervention features and people's profiles affects their adherence. Surprisingly, the ones who could provide researchers with an answer to this question – the intervention participants - are rarely asked. Evidence from the DPP population suggests the disparity between participant-desired program attributes and actual design to be indeed substantial [210]. It appears to discourage participants from repeating their experience. In a follow-up intervention for subjects of the DPP trials, those who had participated in the lifestyle intervention arm were substantially less likely than their treatment-naïve peers to enroll in and continue with an offered follow-up intervention [211]. While the authors speculate about the possible reasons, asking the participants was apparently not part of their study methods.

One observation was, that those lifestyle intervention participants, who had been the least successful with respect to the outcome parameter of weight loss, were also the least likely to enroll in and attend to the follow-up intervention. Inter-individual difference in response to weight loss efforts is an acknowledged issue. When increased physical activity is the mode of choice, the effects range from dramatic weight loss to slight weight gain, the latter of which may be the result of a favorable reduction in fat mass with a concomitant increase in lean mass [212].

Such differential effects are not limited to body weight. Changes in maximal oxygen consumption, following a PA intervention, may range from dramatic improvement to no

improvement at all [213, 214]. If failure to achieve a change in the predetermined outcome parameter is discouraging participants from acquiring a lasting PA habit, the quitters will also miss out on other benefits which associate with increased PA, but which simply remain "below the radar" as they had not been predetermined as outcome parameters.

This narrow focus on a limited number of parameters is borne out of the need of clinical practice for the greatest possible parsimony in determining disease risk, using risk stratification tools such as the Framingham Risk Score (FRS), the metabolic syndrome (MetS) or the PROCAM risk score.

There are however two sides to this coin. A diagnosis of high CVD risk may increase an individual‘s motivation to participate in a preventive intervention, as evidenced in studies which support the notion that the perceived degree of risk is indeed one determinant for participation [210]. The flip side to this is that a diagnosis of low risk potentially reinforces the perception that nothing is wrong with one's lifestyle, thereby negatively affecting the motivation to change it. That would still be tolerable, if our risk prediction tools were sufficiently accurate. But they are not. Most first cases of heart disease and stroke happen in individuals with low to moderate risk, irrespective of the applied risk prediction tool: the metabolic syndrome [56], the PROCAM [57] or the Framingham risk scores [215].

Therefore it could be said that the public health strategy of risk profiling to institute healthy behaviors, may ironically prevent the adoption of such behaviors in the sub-population, which contributes most of the disease cases.

I therefore suggest to substitute, in the sedentary target population, a health profiling, based on a comprehensive set of parameters, for risk profiling. The objective is to account for the multiplicity of phenotypic responses to a HEPA intervention, thereby making visible to the participant (and his health care provider) his moving towards the health end on the health-disease continuum, regardless of where baseline profiling had originally positioned the participant on that continuum. Health profiling thereby carries the potential to exert a greater motivational appeal than the conventional risk-centered approach to health behavior change.

Adding an intervention protocol, which is tailored to each participant's abilities and preferences, will provide for a degree of individualization, the limits of which are set by the boundaries of scientific evidence and operational practicability.

Within these boundaries individualization extends to all aspects of an intervention:

- *intervention objective:* its alignment with each participant's health objective
- *intervention protocol:* its tailoring to each participant's the unique profile
    - her health profile of biophysiological parameters and genetic predispositions
    - her unique set of abilities, skills and preferences
    - the unique profile of environmental demands imposed on her
- *outcome parameters:* a comprehensive spectrum of parameters associated with the health objective, and always including intervention adherence as an essential

outcome parameter in its own right, as PA's effects on health may not necessarily manifest within the chosen physiological outcome parameters

Obviously it is difficult, if not impossible, to realize the proposed degree of individualization within the boundaries set by clinical trial methods and intention-to-treat analyses. But it is precisely because of the latter's stupendous evidence for the benefits of PA that it has now become necessary to translate this evidence into effective PA interventions, even if that demands a deviation from the cherished clinical intervention paradigm. I have argued this case in an earlier publication [216], which coincides with other researchers' calls for redirecting the focus of research from evidence towards dissemination studies [6].

A note of caution: One must keep in mind that public health efforts are directed towards "selling" people on taking up exercise. What makes this sale so difficult is, that physical exercise carries with it the worst possible combination of product attributes any salesman can think of: immediate and continuing cost and a delayed reward.

> This problem is essential to all preventive efforts of public health, which I take the liberty of distinguishing from medical science in the following way: medicine being the science of treating disease with the objective to cure it, public health is the science of treating health with the objective to maintain it.
>
> The one immediate corollary to this distinction is, that public health will always be at a disadvantage when comparing its successes with those of medicine: it is far more difficult to demonstrate who has been spared a disease than it is to show who has been cured from it.

Within this framework the proposed individualization holds the key to (a) reducing the perception of cost (e.g. by matching the target activity to each participant's preferences, skills and abilities) and to (b) accentuating the reward aspect (e.g. by making progress, and hence success, more tangible). With this view, individualization becomes not only a legitimate but an obligate strategy to improve the efficacy of preventive public health efforts.

Practical Implications

Translating the principles of individualization into requirements for the research tool developed for this work, I have defined 5 criteria to be met by each parameter, for it to be considered as a legitimate outcome variable:

- biological plausibility: a causal relation must tie the biomarker to the health status in "dose – response" or threshold association
- significance: published evidence must support the criterion of plausibility

- measurability: standardized assays must permit valid and reliable assessment across laboratories
- modifiability: the biomarker must be modifiable through lifestyle intervention
- utility: parameter measurement and monitoring must be suitable for routine use in clinical practice

Self-Monitoring

General Considerations

Self monitoring is an acknowledged and efficient means to promote adherence to behavior change [217]. In cardiac rehabilitation patients, self-monitoring has shown to increase objectively measured adherence to an outpatient exercise program [218].

It is easy to see how internet-based self-monitoring and record-keeping can provide the key to real-time adherence monitoring by the researcher or clinician. Generally, third-party monitoring has been actively desired by patients in cardiac rehabilitation programs [219], and it has shown to substantially improve adherence in primary care patients who had been prescribed HEPA [220].

The almost ubiquitous reach of the internet has encouraged researchers to evaluate its usefulness to enhance the effects of self-monitoring, with respective trials currently underway [221].

In extension of this idea, internet technology also facilitates telemetry in real-time and across geographic boundaries. The combination of real-time telemetry and telemonitoring is just beginning to emerge as a feasible and cost-effective tool for the remote supervision of heart failure patients' vital parameters [222] and of blood pressure in hypertensives [223]. In these set-ups the internet facilitates the operation of an effective early-warning system with the potential to prevent emergencies and in-hospital treatments.

It is easy to see how real-time monitoring can alert the healthcare provider to adherence decay before the patient/participant is lost to drop-out. Provider efforts to maintain adherence can therefore be focused on exactly those patients/participants who need it, without being wasted on others who don't, as is the case in conventional interventions with periodic group or one-on-one interactions for all.

Internet-based third-party monitoring also gives patients/participants the perception of being watched, a sensation which has shown to strongly influence human behavior [224]. An attractive explanation for this phenomenon is offered by the relatively new error management theory (EMT). EMT proposes that if the survival costs of type-1 and type-2 errors of decision making have been consistently biased over evolutionary history, then ancestral organisms would have been subject to natural selection based on their psychological tendency to make such errors [225]. Mistaking a rustling sound in the forest for leaves in the wind, when the source of the sound is in fact an approaching predator (a type-2 error from the view point of

the predator's soon-to-be lunch), would be far more costly, than mistakenly fleeing from a sound of rustling leaves (a type-1 error).

One can easily translate EMT into the framework of an adherence-monitored HEPA intervention, if we suppose that reputation, being an acknowledged factor in the evolution of human societal interaction [226], is subject to an innate error bias. To the participant, whose reputation of honoring his commitment to intervention goals comes under the perceived scrutiny of a monitoring third party, this scrutiny may engage the participant's type-1 error bias, according to which, adherence to the intervention protocol, when actually not being watched (monitored), is less costly than its type-2 alternative. A further discussion of the potential evolutionary background to this thought is beyond the scope of this manuscript. However, anecdotal evidence suggests, that when third-party monitoring is obviously non-existent, as is the case with automatically and unsupervised generated reminder mails in automated internet-based behavior change programs, adherence to such programs is poor.

> *A note of caution:* When presenting the idea of real-time telemonitoring for the first time to an audience of medical practitioners [227], I was faced with the objection of generating an Orwellian intrusion into the privacy of the patient/participant. On first blush this objection is valid. However, since it is the participant/patient who decides whether, when and to which extent she will avail herself of this monitoring feature, it is reconcilable with valid ethics principles.

Taken together, these observations suggest, that an integration of monitoring principles with modern internet-based telemonitoring abilities will provide a useful aid to improve and maintain adherence in behavior change interventions. A description of the self-monitoring and third-party monitoring is provided in the appendix.

Practical Aspects – What To Monitor

In the model of human energy homeostasis, the brain translates the hormonal signals leptin and NPY into information about caloric reserves and flux. The cognitive model requires parameters that are accessible to rational interpretation. For practical reasons, these parameters ought to be easily measurable by the individual.

Exercise is defined across four dimensions: intensity, duration, frequency and type, the latter consisting of resistance and aerobic modes of exercise.

Intensity is an important determinant for the benefit of exercise, with higher intensity yielding significantly better cardioprotection against CVD [228]. Similar positive associations generally hold true across the dimensions of duration and frequency.

For obvious practical reasons, frequency and duration are the dimensions of aerobic exercise most accessible for measurement by the individual. Objective monitoring of intensity requires

the use of measurement devices, such as heart rate monitors or accelerometers, which complicate the process of self-monitoring, unless and until suitable interfaces have been developed to directly transport the measurement data onto the internet-based monitoring tool. Hence, under current prevailing conditions, it will be more feasible to code the desirable exercise intensity into the volume and frequency prescription which simplifies the monitoring process.

If resistance training is a behavioral goal, frequency of sets and repetitions will be the monitoring parameters. Again, intensity expressed as weight or resistance, can be coded into the prescription to achieve the desired volume.

Continuity

General Considerations

It has been suggested that the high prevalence of sedentism is at least partly attributable to research being focused mainly on the adoption of exercise rather than its maintenance [229]. The predominance of limited-duration interventions clearly supports this contention. This is unsurprising, given that acute care continues to be the paradigm of our health care system, which has evolved from the need to treat acute diseases, not to prevent the chronic varieties. However, inherent to the proposed model of human energy homeostasis is the perpetuation of a cognitively controlled feedback loop as an essential prerogative for its maintenance. Given the constant exposure to the seductions of sedentary lifestyles, intervention continuity is a necessity for sustained success. This argument is strengthened by the observations that (a) large numbers of attendees drop out within latest 3-5 years after a one-time intervention [121] and (b) long-term change in metabolic risk factors is as informative and predictive of risk as are absolute values of risk factors [230].

There are two obvious caveats to these considerations: cost and resource constraints.

The costs for conventional interventions are indeed high [231, 232]. That, however, must not distract us from the need for lifelong intervention, as outlined above. Rather should it stimulate research into the utility of newly emerging technologies, such as the internet and telemetry, and their potential contribution to optimize the cost-benefit ratio of open-ended HEPA interventions.

Specifically the internet, with its unique communication platforms, has demonstrated the ability to amalgamate the input of geographically dispersed experts into coherent outputs, as is the case in networks such as wikipedia. There is no reason to assume, that we will not be able to consolidate the contributions of varied health science specialists and care and service providers into one network of preventive lifestyle change interventions, in which each expert group provides the care and services of its competence domain, thereby relieving the primary care physicians from tasks which would otherwise impose on their resources, if such interventions were to be delivered within the conventional framework of health care.

Practical Implications

In the proposed open-ended interventions, the objective is to keep the cognitively controlled feedback loop operational with the intended consequence of maintaining a PA behavior that has been agreed to by the participant. Active self-monitoring is the indicator of this feedback loop being operant. Its parameters (discussed in the preceding paragraph) provide the quantitative PA data that are necessary to investigate the strength of their correlation, if any, with health outcome parameters (discussed under the subject “individualization” above) and to consequently inform optimization strategies. Hence, the parameters of self-monitoring become the independent variables, with which the research questions shall be addressed, specifically whether:

(a) during an initially limited period of observation, self-monitoring generates a degree of adherence to HEPA behavior which is sufficiently large to suggest that the intervention model will, in an intervention of unlimited duration, improve effectiveness compared to conventional interventions.

(b) self-monitoring correlates with clinically relevant health benefits in self-monitoring participants

If the results indicate positive answers to both questions, follow-up research in an intervention of unlimited duration is warranted.

AIMS AND OBJECTIVES

This work pursues two investigative objectives: namely (a) the translatability of the principles of individualization and self-monitoring into a practically feasible intervention which yields significant improvements of physical activity habits in previously sedentary adults, and (b) the evaluation of measurable intervention effects (if any) and their comparison between follow-up and baseline and between participant groups.

With a specific view to the underlying model of a cognitively controlled feedback loop, which is hypothesized to be necessary for the activation and maintenance of adequate physical activity habits, the study has been designed to answer the following research questions:

(1) Under conditions closely approximating feasible real-life program delivery, will an intervention, which is based on the aforementioned principles of individualization and self-monitoring, activate and maintain the required cognitively controlled feedback loops in a sufficient number of participants to:
    a. compare favorably with published adherence rates for physical activity interventions?
    b. justify investigating the effects of intervention continuity in a larger and longer term follow-up investigation?

(2) Will participants with an activated feedback loop witness statistically significant and clinically meaningful improvements of physiological CVD risk parameters compared to
    a. baseline measurements?
    b. non-adherent participants?

DEVELOPMENT OF THE HYPOTHESES

The objective is to formulate testable hypotheses, which refute or favor the proposed theory and tool. Systematic self-monitoring ought to engage a cognitively controlled feedback loop, which facilitates the uptake and maintenance of an agreed individualized exercise curriculum in a large enough proportion of the study population to suggest potential public health merit.

The effect of the intervention on parameters of physical fitness (the objectively measurable and risk relevant correlate of PA) and energy homeostasis ought to be large enough to suggest significance and clinical relevance.

The hypotheses specified hereinafter were tested in a PA intervention, the details of which are described and discussed in a subsequent section of this paper. The following are the intervention details required to understand the hypotheses that were tested in this intervention, which lasted for 6 months.

> The study population consisted of 117 Caucasian participants (33 women), who were enrolled into this prospective, nonrandomized exploratory intervention designed to improve physical activity status in sedentary adults through individually prescribed exercise programs. Individual health profile parameters, exercise goals and progress were monitored in an internet based application, which was specifically developed to deliver this intervention, with a view to making available the use of this tool to other research groups in the future. To facilitate the self-monitoring of exercise progress, the exercise curriculum, which had been individually agreed with every participant at the start of the intervention, was translated into a point score. Participants earned one point for every 5 minutes of endurance exercise performed at an individually prescribed intensity based on an ergospirometrically determined exercise capacity. The minimum volume and frequency of endurance exercise, which had been agreed with every participant, consisted of thrice weekly 20 minutes of high-intensity interval training (HIT), the rationale for which is explained in the methods section. Participants whose body composition analysis had suggested potential health benefits to be accrued from resistance exercise had been encouraged to perform the latter in addition to their agreed curriculum of endurance exercise. Within the relevant point scoring system, participants earned one point for every set (consisting of a target number of repetitions) of exercise, with typically 2 sets of 8 different exercises to be performed at least twice weekly.
>
> Participants could enter their point score either directly via access to a secured website or via a mobile-phone based applet. Points were cumulatively entered for 4 consecutive 6-week periods. Automated and preset alarm functions (email) alerted the investigator about lack of a participant's login (7 consecutive days without login prompted an alarm) and/or probable failure to reach the agreed 6-week point score. Each prompt initiated a direct and personal follow-up (email, phone call) with the

participant to investigate the reasons. At the end of each 6-week period a review of achieved point scores determined whether the exercise goals needed re-adjustment.

All analyses performed at baseline were repeated at follow-up.

Hypothesis 1: Adherence

The proportion of actively self-monitoring participants at the end of intervention is 75% or better, with the minimum criterion being a recorded weekly duration of endurance exercise (volume aspect of adherence) of 60 minutes (3 x 20 minutes of high intensity interval training) or more for at least 12 consecutive weeks (duration aspect of adherence), with the last self-reported login not earlier than 1 week (latency aspect of adherence) prior to the date of final assessment.

Rationale For The Definition Of Adherence

Typically the degree of adherence to an intervention trial determines the intervention dose to which a subject will have exposed himself at the time of follow-up. This is an important aspect of establishing the strength of the association between the intervention and its hypothesized outcome. It does not answer the question whether and to which degree adherence is sustainable in free-living individuals. That is the question of this intervention trial. It *a priori* accepts an association to exist between PA and health outcome. What it attempts to answer is whether the intervention strategy which is specifically aimed at making adherence to PA sustainable, will, at the time of follow-up, see a large enough proportion of participants availing themselves at follow-up to PA at a large enough dose and having done so over a long enough duration that the accrued measurable health benefits support subjecting this intervention to larger and longer-term prospective follow-up investigations upon its chronic public health benefits.

To put it simply: while preceding trials have established the effect of taking the medicine (PA), this trial begins to investigate how to make people keep taking it.

Underlying this hypothesis is the proposed model's postulate that self-monitoring reflects an operant controlled feedback loop (CFL+), the engagement of which is essential to maintain human energy homeostasis. The objective is to increase the prevalence of CFL+ in a given population to markedly reduce the burden of hypokinetic diseases.

The three-quarter adherence rate is admittedly an arbitrary value, as there are, to the best of my knowledge, no data available which would provide a comparison benchmark from similar study designs and objectives.

CFL+ is also quantifiable by virtue of the underlying parameters of duration and volume of PA. To investigate the association of CFL duration with the outcome parameters of hypotheses 2

and 3, the relevant analyses were performed with participants being stratified according to three different periods of CFL duration (90 days, 120days and 150 days). The terms CFL+ and CFL- were used to describe the groups of participants meeting or not meeting the adherence criteria respectively, being synonymous with the terms “adherent” (CFL+) and “non-adherent” (CFL-).

The platform developed for this research effort, is to be used as a tool for the delivery of open-ended PA interventions in varied populations. In these populations, the prevalence of CFL+ as the drivers of HEPA behaviors can serve as an essential correlate for disease prevalence.

This will provide for more detailed insights into the association of CFLs and PA with disease incidence and prevalence in target populations. The latter may be the patients of a primary care practice, post-event rehabilitation patients of a hospital, the employees of a corporation, or a health insurer’s policy holders. In any case, the populations are open, with new members entering, and existing members leaving them over any period of time.

Measurable changes in modifiable biochemical and anthropometric parameters of risk are a desirable intervention effect. Hence the secondary hypotheses will address intervention effects on such parameters.

Hypothesis 2: Intervention Effect On Physical Fitness

CFL+ participants (adherent) will show significant improvements of measures of physical fitness from baseline to follow-up, with these changes being significantly different from changes (if any) observed in the CFL- group (non-adherent).

Hypothesis 3: Intervention Effect On Parameters Of Body Weight

Overweight CFL+ participants (BMI>=25) will show significant improvements in weight status from baseline to follow-up, with these changes being significantly different from changes (if any) observed in the CFL- group over the same observation period.

Hypothesis 4: Intervention Effects On Parameters Of Cardiovascular Risk

CFL+ participants will show significant improvements in blood lipid measures and related measures of CVD risk (PROCAM risk score) with these changes being significantly different from changes (if any) observed in the CFL- group over the same observation period.

OVERALL STUDY DESIGN

"If you want to truly understand something, try to change it" Kurt Lewin

This study is a non-randomized exploratory intervention trial that tests the efficacy of a web-based lifestyle intervention tool (Electronic Lifestyle File – ELF) designed to

(a) promote adherence to individualized lifestyle change interventions through monitored self-monitoring with the objective to …

(b) reduce the risk of cardiometabolic disease.

Subjects were recruited from among German holders of a compulsory health insurance policy who had taken up their insurer's invitation to participate in a subsidized fitness and physical activity examination.

Main inclusion criterion was a self-reported current volume of leisure time physical activity (LTPA) of 1 hour or less per week. All participants were Caucasians of German extraction.

Following enrollment, participants were assessed at baseline and after 6 months on biochemical parameters, parameters of physical fitness and body composition. Throughout the intervention, participants' adherence to an individualized LTPA protocol was monitored via a web-based electronic lifestyle file (ELF). Personalized prompts were given to participants whose lack of progress reporting suggested decay of adherence.

DETERMINATION OF SAMPLE SIZE

For the calculation of sample size and power, two aspects of the study design need to be considered:

- A recruitment strategy potentially engaging self-selection bias.
- An *a priori* sample size of 120 participants, which was based primarily on budgetary constraints and logistical considerations.

These two aspects warrant sample size and power calculations which address the questions of (a) whether and to which degree any potential difference between the sample population and the underlying population is detectable, and (b) whether the hypothesized changes of outcome parameters can be reasonably detected within the given sample size constraints.

Sample Size Calculations to Asses Potential Selection Bias

Based on the given sample size of 120 participants, power calculation was used to determine the minimum parameter difference detectable as constituting a significant difference between the ELF sample and the reference population.

Parameter values for the reference population were taken from data published by the World Health Organization (WHO) and drawn from the MONICA study populations as published in the MONICA Population Survey Data Book [233]. The MONICA (Multinational **MONI**toring of trends and determinants in **CA**rdiovascular disease) Project was established in the early 1980s in 21 nations with altogether 32 collaborating centers, 4 of which had been set up in Germany (Augsburg, Bremen, East Germany and Rhein-Neckar/Heidelberg). The project's objective was to investigate diverse trends in cardiovascular disease mortality and morbidity. BMI data were cross-checked with data published by the German Federal Demographic Authority (Statistisches Bundesamt) and accessible online [234]. The reference age group of 45-54 years was selected based on information about mean age obtained from the personnel department of Siemens AG about the mean age of employees on location (45 years). Table 1a presents the minimum parameter differences, necessary to determine significance of difference between the MONICA cohort and the ELF sample (at baseline). MONICA reference values were taken from the male cohorts aged 45-54 years, as the ELF participants were expected to be predominantly men in that age bracket.

All calculations were carried out using Intercooled STATA 11 for Macintosh (Stata Corp. Texas, U.S.A.), which uses the following formula for determining the required sample sizes for two-sample tests of equality of means:

Equation 1: $$n1 = \frac{\left(\delta_1^2 + \delta_2^2 / r\right)\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\left(\mu_1 - \mu_2\right)^2}$$

where α is the significance level, 1-β is the power, $z_{1-\alpha/2}$ is the (1-α/2) quantile of the normal distribution and r=n2/n1 is the ratio of the sample sizes.

Table 1:

Determination of power and minimum parameter differences, necessary to determine significance of difference between the MONICA population and the ELF sample

	MONICA Mean (SD) [a]	Minimum Difference	Power[b]
BMI (kg/m^2)	27.3 (3.5)	1.2	0.85
HDL-C (mg/dL)	47.5 (14.7)	5	0.84
TCH (mg/dL)	241.3 (47.5)	16	0.83
Proportion (%) of HDL-C in TCH	20.27 (6.99)	2.5	0.87

a: Reference values taken from the German MONICA Augsburg urban Reporting Unit Aggregate [233] for men aged 45-54

b: given the sample size of 120 participants, and calculated for α=0.05, two-sided

Sample Size Calculations for Hypothesis Testing

The primary outcome variables of this investigation are (a) the proportion of subjects with an operant cognitively controlled feed back loop (CFL+) at follow-up (adherence), and (b) the change of peak oxygen consumption (VO2peak) and body weight parameters from baseline to follow-up within and between CFL groups (adherent vs. non-adherent). Secondary outcome variables are the within- and between group changes of HDL-C, TCH, TCH/HDL ratio LDL-C and Triglycerides.

Sample size and power calculations require assumptions to be made about the effect size and the standard deviation of the change of parameters under investigation.

These assumptions are as follows:

1. Hypothesis 1: Percentage of CFL+ participants at follow-up is 75%

   The alternative hypothesis (refer to hypothesis 1 above) of 75% adherence is contrasted with (a) a 50% drop-out, typically observed across clinical exercise interventions within the first 6 months (as discussed in the preceding sections), and (b) with the close to 60% adherence rate observed in a comparable 24-weeks worksite intervention, which consisted of 3 weekly 20-minutes high intensity aerobic workouts in addition to strength training [235].

2. Hypothesis 2: Improvement of VO_2peak

   At 1 MET increments, cardiorespiratory fitness (CRF) has been found to linearly correlate with a decreased risk of CVD events in a population of Finnish men (1294 men) of similar mean age of 51.8 years [236]. The mean and SD of VO_2peak in this population was 32.5 and 7.5 ml/kg/min respectively.

   The power calculation for within and between group changes are based on the assumptions of an approximate 1-MET change in the CFL+ group vs. no change in the CFL- group. The SD for the 1-MET change is expected to be 4 ml/kg/min. This value is based on personal experience from several years of CPET practice and evaluations of practice data. It was chosen because most published studies provide dispersion statistics for pre and post means but not for the paired differences.

3. Hypothesis 3: Improvement of body weight status

   A reduction of 1 BMI unit was considered the desirable minimum effect size to be detectable in the CFL+ group of participants. This value was based on several assumptions. Since the recruitment strategy was focused on enrolling primarily sedentary and overweight adults the mean BMI at baseline was expected to be at least 28 kg/m^2. Based on the mean height for the underlying population as published by the German Federal Office of Statistics (Statistisches Bundesamt) from the 2005 German Microcensus, the mean height for German men in the 45-54 age cohort is 1.78 m. This translates into a mean body weight of 88.7 kg, given the expected BMI. The minimum weekly PA requirement of 60 minutes of moderate intensity aerobic

exercise was expected to be performed predominantly by jogging/running, the energy expenditure of which has been estimated to be 7 MET [237], one MET being equivalent of 3.5 ml/kg/min oxygen consumption. Thus, an approximate weekly energy expenditure of 60' x 7 METs = 420 MET-minutes, or 130 liters of Oxygen, would be expected. With 1 L O_2 being the equivalent of 5 kcal [238], this translates into a weekly energy expenditure of approximately 650 kcal. Thus, over a period of 24 weeks 16,000 kcal could be expended. With the calorific value of 1 kg of fat being approximately 7,000 kcal, a weight loss of ≈ 2.5 kg could be expected. This weight loss equals 0.8 BMI units for a person of the aforementioned height and weight. The published results of the DEW-IT weight loss trial suggest a SD of 0.6 for a BMI change of -1.9 in the intervention group [239]. For the sample size calculation this reference SD value was arbitrarily doubled to 1.2. The rationale being, that, while weight loss was the DEW-IT intervention's target outcome, in the ELF intervention weight loss is hypothesized to be a coincidental outcome and secondary to a targeted increase of CRF. Under these circumstances, a greater variance of BMI change values is to be expected. Also, the DEW-IT intervention group size was very small (N=22). Taken together, these aspects warrant the assumption of a larger variance of the weight change parameters in the ELF sample.

4. Hypotheses 4: Improvement of Blood Lipid Parameters

   Desired effect size was defined as a 10% change from baseline values. The underlying rationale is the observation that studies of physical activity interventions report modest and often non-significant improvements of blood lipid parameters of generally less than 10% from baseline [240-242]. HDL was chosen as the sole test parameter, as improvements of blood lipid parameters have been reported in response to higher caloric exercise for HDL and TCH/HDL ratio, with TCH and LDL not changing significantly [241, 243]. Published studies typically report the dispersion statistics at baseline and follow-up, but not the variances for change of lipid parameters nor the t-values of the paired analyses. For reference purposes the variance values for paired differences were taken from an investigation into the effects of physical activity on HDL in 269 men and women aged >=50 [244].

To investigate adequacy of the sample size to detect significance of the difference in proportion of adherent subjects (defined as the number of participants meeting the CFL+ criteria) between the ELF sample and the aforementioned reference worksite intervention [235], a one-sample test of proportion was conducted using Intercooled STATA software.

The underlying formula is shown in equation 2

Equation 2: $$n = \left[\frac{z_{1-\alpha/2}\left(p_0\{1-p_0\}\right)^{1/2} + z_{1-\beta}\left(p_A\{1-p_A\}\right)^{1/2}}{p_A - p_0} \right]^2$$

Where n is the sample size, the null hypothesis is $p=p_0$ and the alternative hypothesis is $p=p_A$, 1-β is the power, and $z_{1-\alpha/2}$ is the (1-α/2) quantile of the normal distribution.

The proportion of 0.6 was set as the null hypothesis, with the alternative hypothesis being 0.75.

At α=0.025 and power of 0.9, two-sided the required sample size is 114.

To investigate whether the *a priori* sample size was adequate to detect significance of the expected differences of means compared to the null hypothesis, one-sample tests for power and sample size were conducted using Intercooled STATA software. The underlying formula for calculating sample size and power is as follows:

Equation 3a: $$n_1 = \frac{\left(\delta_1^2 + \delta_2^2 / r\right)\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\left(\mu_1 - \mu_2\right)^2}$$

where δ is the standard deviation, μ is the mean, $n_2=rn_1$, 1-β is the power, and $z_{1-\alpha/2}$ is the (1-α/2) quantile of the normal distribution.

Power was set to 0.9 with a one-tailed significance level α=0.05

Table 2 presents the results of the analyses expressed as (a) sample sizes required to detect the hypothesized intervention effect sizes, and (b) power provided by the given size of the study sample (N=120), with both calculations based on the hypothesized ratio between adherent and non-adherent participants r=3.

Table 2:

Sample Size And Power Calculations For Hypothesized Between-Group Differences Of Means

	Difference in Change[a]	required sample size		power[c]
		non-adherent	adherent	at given N=120
Adherence (%)[b]	15%	21	62	0.97
VO_2peak (ml/kg/min)	3.5	15	45	0.98
BMI (kg/m^2)	0.8	26	78	0.99
HDL (mg/dL)	4	58	74	0.61

Note:
a: for hypothesized between-group differences of change from baseline to follow-up, with within-group change of = 0 for non-adherent group; does not apply to the parameter "adherence", see note *b*
b: 75% hypothesized adherence compared to the 60% evidence-based postulate
c: for given sample size N=120
* α=0.05, β=0.1, one-tailed

The results of the power and sample size analyses demonstrate that, though logistically restricted, the sample size was adequate to detect clinically meaningful changes of this study's primary outcome parameters of cardiopulmonary fitness and body weight status.

The power calculation for HDL indicated inadequate power to detect an intervention effect of the minimally expected effect size on adherent participants, compared to their non-adherent peers. However, the power calculations were based on simple t-test, not taking into consideration the correlation between intra-individual baseline and follow-up measurements, which improves the variance of the estimate of the intervention effect. Assuming such correlation to be 0.7, instead of the 0.5 as assumed by t-testing, the power is increased to 80%. This estimation is based on the following equation for the calculation of improvement of variance in repeated-measures designs [245]:

Equation 3b: variance improvement = $$\frac{1+(r-1)\overline{\rho}_{post}}{r}+\frac{1+(p-1)\overline{\rho}_{pre}}{p}-2\rho_{mix}$$

where *p* is the number of measurements at baseline, *ρ* is the correlation between measurements at baseline (pre), at follow-up (post) and between measurements at baseline and at follow-up (mix) respectively.

EXECUTION

This study was conducted at an industrial park (Siemens Industriepark Karlrsuhe, SIK) located in the city of Karlsruhe of the South-Western German state of Baden-Württemberg. During the study period, approximately 5.000 white and blue collar employees were working on-site, most of which had enrolled in the health insurance plan of Siemens Betriebskrankenkasse (SBK), a German provider of a comprehensive health insurance coverage that is compulsory to have for every resident in Germany. The study participants were recruited from among the 200 individuals who had accepted an offer of SBK to participate in a fitness assessment campaign at a subsidized rate. The campaign was directed at sedentary individuals insured with SBK and interested in a sports-physiological assessment of their physical fitness levels through cardiopulmonary exercise testing (CPET).

ETHICAL COMMITTEE AND INFORMED CONSENT

The study protocol was approved by the ethics committee of the state medical board (Landesärztekammer) of Baden-Württemberg. Informed consent was obtained in writing from all participants at the initial consultation and prior to the baseline assessment .

RECRUITMENT

SBK invited all 200 respondents to three public 60-minutes presentations delivered by the author on subjects of physical activity, diet and health over 2 months at an on-site venue. The purpose of these presentations was to raise participants' awareness of physical activity being a determinant of cardiovascular health. At the same time the purpose of the study intervention, its exclusion and inclusion criteria were explained and attendees' questions were answered. Attendees were also provided a set of enrollment forms, consisting of a detailed explanation of the study purpose and procedures, a health history questionnaire, an informed-consent form and a declaration-of-participation form (see appendix 3). The invitation was expressed to all attendees who were interested to participate in the study and who believed to meet the inclusion criteria to make an appointment with the investigator for a personal consultation and assessment of suitability to enroll.

Altogether 150 persons responded to the invitation. Of these, 33 individuals could not be enrolled in the study, primarily for not meeting the condition of being sedentary, with 60 minutes or less of weekly structured leisure time PA (28 individuals), for having been notified of an impending transfer to another city (4 individuals) or for being physically handicapped (1 individual). The remaining 117 individuals were enrolled into this study.

PARTICIPATION CRITERIA

Principles applied to the selection of participants:

- to ensure selection of sedentary participants
- to ensure selection of participants with the ability to participate in and comply with a physical activity intervention
- to avoid confounding effects on the primary outcome measures (adherence and biological effects)
- to prevent adverse events from participation in the physical activity intervention

Inclusion Criteria

- Ethnicity: Caucasian
- Gender: male and female
- Age: lower age limit of 25 years with no upper age limit
- Physical activity level: self reported LTPA of less than 1 hour per week
- BMI: lower limit of 19 with no upper limit

Exclusion Criteria

Objective	Exclusion criteria
to ensure selection of sedentary participants	currently exercising at a level that equals or exceeds the intended volume and intensity of exercise
	Recent (within past three months) history of myocardial infarction, stroke or TIA or major surgery
	orthopedic limitations which would prevent from participation in an exercise program
to ensure subjects' ability to participate in a physical activity intervention	Asthma and or other lung disease which limits the ability to perform exercise at high intensity (80-95% of VO_2peak
	Osteoporosis, arthritis, diseases of the liver, kidney or thyroid which would prevent from participation in an exercise program
	peripheral arterial disease which limits the ability to walk
	pregnancy
to avoid confounding of or interference with study results independently of subjects' participation	drug or alcohol abuse
	current participation in another lifestyle change intervention
to avoid exposing subjects to health risk	uncontrolled or poorly controlled hypertension (SBP >= 160 mmHg and/or DBP >= 100 mmHg)
	uncontrolled or poorly controlled diabetes mellitus

MEASUREMENTS

All measurements described hereinafter were performed in accordance with the study schedule presented in Figures 3a &b.

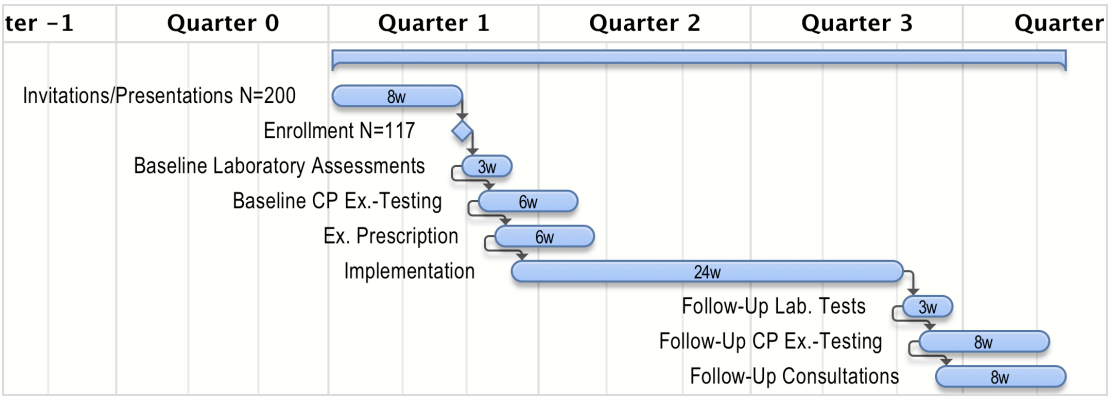

Figure 3a. Overall Study Execution and Time Table of Measurements

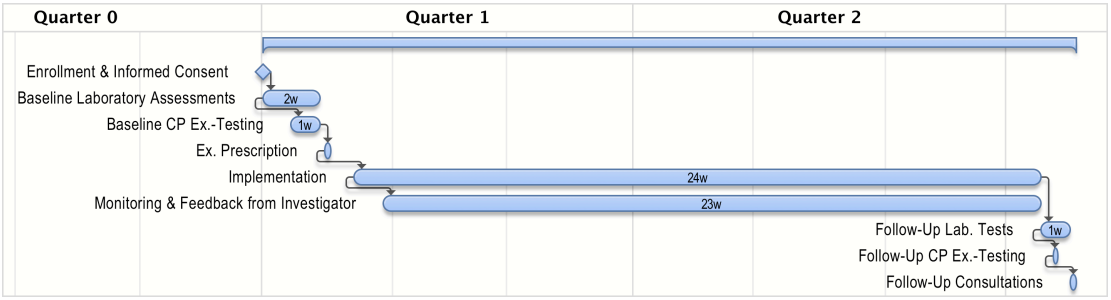

Figure 3b. Study Execution and Timetable of Measurements as Experienced by the Participants

Determination Of Levels Of LTPA

The gold standard for the objective measurement of volume and intensity of physical activity is the doubly labeled water method.

While the assessment of physical activity levels through questionnaires is an accepted tool in epidemiological studies, low correlation between questionnaire data and objectively measured energy expenditure has been found on the level of the individual [246, 247]. The suggestion has therefore been made to use questionnaires as a tool for classification of physical activity levels rather than for the purpose of estimating energy expenditure [248]. As such, simple one- or two-item questionnaires have shown to provide suitable reliability in classifying the respondent as a sedentary or more active individual [249]. As it was the objective of this study to recruit sedentary individuals a question was used, which, from the author's working experience, provides reasonably reliable indication about the time spent in moderate- to high-intensity LTPA: "Think of an exercise for which you usually wear exercise

clothing and which you perform at an intensity that forces you to increase your breathing rate to the point at which you would find it difficult or impossible to maintain a normal conversation. Do you spend more than one hour per week in such exercise at the described intensity? A negative answer to the question was a necessary inclusion criterion.

With respect to the assessment of subjects' LTPA habits it is imperative to recall what is the study aim and what it is not. The research aim is not a comparative objective assessment of subjects' volume and intensity of LTPA before and after intervention. Rather is it the question whether the studied intervention is (a) able to promote adherence to an LTPA curriculum whose beneficial health effects have been established in peer reviewed research, and (b) whether a self-reported degree of adherence to this curriculum correlates with clinically relevant improvements of objectively measurable markers of cardiometabolic health. This distancing from objective LTPA assessment would be superfluous if the latter was a straightforward exercise of measuring a vital parameter, economically and practically feasible for large-scale application. However, valid and reliable measurement of (a) physical activity and (b) the intensity at which it is performed has remained a difficult issue with several available methods each having its own advantages, draw-backs and limitations. The following discussion is to highlight these issues and to support the contention implicitly made here, namely that neither of the available techniques will add clinical or practical value to the study results.

PA measurement techniques may be grouped into three categories: direct and indirect objective measurement, and subjective measurement techniques. The underlying principle of the direct objective measurement is that all physical activity inevitably requires the expenditure of energy.

Direct calorimetry, the most accurate method of determining energy expenditure, measures the heat into which the chemical energy utilized for physical activity is degraded, thereby providing a direct measurement of a body's metabolic rate.

Indirect calorimetry measures oxygen consumption, carbon dioxide production and nitrogen excretion to calculate energy expenditure.

For both methods metabolic chambers can be deployed in which study subjects may remain for any extended period of time. Cost and logistical considerations limit the application of metabolic chambers to specific study questions, which require relatively few study subjects.

These techniques are certainly of no use in research projects where intervention effects in free-living individuals are the outcome measure.

Indirect calorimetry can be performed through breath-by-breath analysis of gas expired through a face mask and connected to suitable oxygen and carbon dioxide sensors. This technique also requires costly laboratory equipment, the attendance and operation of suitably

skilled clinicians and is therefore limited to clinician supervised study situations, though suitable for higher subject throughput than metabolic chambers.

Another form of indirect calorimetry is the doubly labeled water (DLW) technique, mentioned above [250]. With this method, subjects are to ingest a standardized amount of the two stable isotopes deuterium and oxygen(18) as water. The isotopes equilibrate with body water and are eliminated from the body at different rates: deuterium leaving the body as water only, whereas O(18) leaving as water and as CO2. The greater the difference in the elimination rates the greater the CO2 production, hence the larger the energy expenditure. While this method provides reasonably accurate estimates of energy expenditure [251], it only measures total energy expenditure and does not provide for a differentiation of energy spent at various intensity levels of PA. Furthermore, production and analysis of the isotopes is expensive. All these factors make the DLW technique unsuitable for the project at hand.

Measurements Of Vital Signs At Baseline And At Follow-Up

Blood pressure measurement was made in duplicate after 5 minutes of rest in a well-ventilated room at about 24^0 C on both arms with the participant in the supine position. The mean of both measurements was considered for analysis.

Body weight and standing height were measured in light sports clothing and without shoes to the nearest 0.1 kg and 1 cm, using an anthropometer and a calibrated electronic scale, respectively. BMI was calculated as the ratio between weight and height squared (kg/m^2).

Body composition was measured using an impedance analyzer device and software (BIA 2000-S, Data Input, Frankfurt, Germany) for tetrapolar BIA measurement of resistance (R) and reactance (Xc) at frequencies of 5, 50 and 100 kHz. Measurements were made at the right side of the subject between the wrist and ankle while in a supine position and after having rested for 5 minutes. The equipment, analytic algorithms and the measurement protocol have been validated previously in comparable populations [252, 253].

All biochemical parameters were determined by standard laboratory methods using certified assays in a local clinical laboratory. The Siemens company medical officer sampled venous blood in EDTA tubes in the morning between 07:30 and 08:45 after an overnight fast for the analysis of total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides and fasting glucose.

Venous blood sampling was repeated for the first 61 subjects within 7-10 days following the initial assessment. Subjects were instructed not to change any of their lifestyle habits during this period.

Rationale For Repeated Blood Measurements

The purpose of this repeated measurement was to determine the variability of standard biochemical parameters and to subsequently assess the reliability of before-and-after measurements of such parameters as markers of intervention effects.

Intra-individual variability of lipids, lipoproteins and apolipoproteins contributes to the less than reliable prediction of cardiovascular risk [254-260]. This may complicate efforts to correlate changes in PA with changes in cholesterol levels [261], the latter being of rather modest magnitude of <10% for blood lipids [241, 242] and lipoproteins [240].

Exercise Testing

Exercise testing, performed as cardiopulmonary exercise test (CPET) on a cycle ergometer, was the integral component of the health insurer's fitness testing promotion for the execution of which the author's laboratory had been contracted on-site. Each exercise test had been carried out under proper medical supervision.

All exercise tests were performed in a well ventilated room at a temperature of about 24^0 C. Participants had been instructed not to consume alcoholic beverages and not to eat a heavy meal or participate in any vigorous physical activity 24 h before the test. Before each test, subjects were also instructed on how to perform the exercise test.

Special emphasis was placed on the instruction to alert the tester immediately to any untoward sensation such as dizziness, chest pain, joint pain or to any other reason for which the participant would want to terminate the test immediately. Participants were also informed that the tester would terminate the test if observed clinical evidence were suggestive of distress.

Indicators for distress were defined in accordance with current ACSM guidelines [262], specifically

- onset of angina-like symptoms
- >= 20 mmHg drop in systolic blood pressure or failure of systolic blood pressure to rise with increased exercise intensity
- excessive rise in systolic (>260 mmHg) or diastolic (>115 mmHg) blood pressure
- signs of poor perfusion
- failure of heart rate to increase with increasing exercise intensity
- non-physiological change in heart rhythm

Barring any such event, participants were encouraged to continue the test until they reached exhaustion.

Tests followed a ramp protocol to exhaustion on a cycle ergometer (Customed, Germany) with the ramp increment chosen, based on age, weight, height and training history, as to reach exhaustion within 8 to 12 minutes [263]. For the first 3 minutes the workload was fixed at 5 W. After termination of the test, regardless of reason, participants continued to cycle at minimal resistance of 5 W for another 2 minutes to monitor recovery of heart rate and blood pressure.

The resistance on the cycle ergometer was controlled by the ergospirometric software (Cortex, Leipzig, Germany) to be independent of pedal cadence.

Spiroergometry was carried out using a breath-by-breath-system (Cortex MetaLyzer 3B, Leipzig, Germany), which has been validated previously [264]. Expired air was collected continuously using a facemask. The system was calibrated prior to each test in accordance with manufacturer's guidelines using a 3-L syringe for volume calibration and ambient air measure for gas calibration.

During all tests heart rate was recorded with a wireless chest strap telemetry system (Polar, Kempele, Finland). Blood pressure was measured every three minutes oscillometrically using a Customed BP measuring device integrated into the CPET equipment and software. Simultaneous gas exchange measurements consisted of minute ventilation (V'E), oxygen uptake (V'O2; electrochemical cell), and carbon dioxide output (V'CO2; infrared analyzer). For calculations, data were averaged over every 20 seconds.

Determination Of VO2peak

Peak oxygen uptake (VO_2peak) was defined as the highest value for oxygen uptake averaged over 20 seconds. The most common reasons for stopping the exercise test were leg fatigue and breathlessness.

Determination Of Anaerobic Threshold

The anaerobic threshold (AT) is defined as the exercise rate above which the aerobic mitochondrial production of ATP is supplemented by ATP production from incomplete anaerobic breakdown of glycogen to pyruvate [265]. Buffering of the resulting increase in lactic acid leads to a net increase in CO2 in the blood within a few seconds of reaching this threshold. In expiratory gas analysis this event manifests (a) as an acceleration of CO2 expiration in comparison to O2 consumption, providing for the “V-slope method” of threshold determination, and (b) as an increase in ventilatory volume relative to O2 consumption while initially maintaining the ratio of ventilatory volume to CO2 expiration, thereby providing for the “ventilatory equivalent method” of threshold determination [265].

To determine the participants’ individual anaerobic thresholds, the following steps were performed sequentially after each exercise test:

(1) 20-seconds averaging of all ergospirometric data

(2) initiating the ergospirometric analysis software’s automatic V-slope calculation function to perform a regression analysis of the slopes of the VCO2/VO2 curve

(3) visual inspection of the ventilatory curves and of the position of the automatically calculated AT

(4) manual correction of the calculated AT if visual inspection indicated a discrepancy between automatic calculation and true AT.

Samples for a automatically calculated AT and manual corrections are provided for illustrative purposes in Annex “X”.

STATISTICAL MEASURES & PROCEDURES

The statistical methods were chosen in accordance with accepted principles as described by Altman [266] and Rosner [267].

Baseline Comparisons

To evaluate the effect of small sample sizes on the power to detect significance of parameter differences between the adherent and non-adherent groups at baseline, effect sizes were calculated and expressed as Cohen’s *d* using equation 4.

Equation 4: $$d = \frac{m1 - m2}{\sqrt{\frac{(n_1 - 1)s_1^{\,2} + (n_2 - 1)s_2^{\,2}}{n1 + n2}}}$$

where m1 = mean of group 1; m2 = mean of group 2; n1 = number of observations in group 1; n2 = number of observations in group 2; s1 = SD of group 1; s2 = SD of group 2; and the expression in the denominator is the *pooled standard deviation, "pooled SD".*

Cohen suggested to categorize effect sizes as "small", "medium" and "large" for *d* values of 0.2, 0.5 and 0.8 respectively [268].

This line of investigation served to identify potential insufficiencies of sample size to detect true parameter differences between non-adherent and adherent groups at baseline. The combination of large effect size with a t-test returning non-significance of difference was taken as such indication, warranting further investigation.

This comparison of baseline parameters between adherent (CFL+) and non-adherent (CFL-) groups was deemed necessary to answer the question whether these two groups differed from the outset by some parameter, which may have had a causative effect on the adherence status at follow-up. Given the 13 parameters (age, VO_2peakweight, body fat, BMI, TCH, LDL, HDL, TG, TCH/HDL ratio, systolic and diastolic blood pressure, PROCAM score) the possibility of the family-wise type I error needed to be considered. In the context of this investigation, it is the probability that even if the adherent group does not differ from the non-adherent group at baseline (the null hypothesis), the chance of finding one of the 13 comparisons being significant is no longer 0.05 but 0.48, with the formula for the error rate across the study being [269]:

Equation 5: $$1 - (1 - \alpha)^n$$

where α is the significance level and n is the number of tests performed.

Accepting the Bonferroni adjustment would require a significance level of p<0.0039,which is derived from the formula:

Equation 6: $$1 - (1 - \alpha)^{\frac{1}{n}}$$

Despite these considerations, Bonferroni adjustment was omitted for the number of tests (13) performed for significance of baseline differences between CFL- and CFL+ groups for the reasons that (a) no null-hypothesis with respect to between-group baseline differences had been formulated *a priori*, (b) the parameters cannot be considered to be independent of each other (e.g. lipid levels and blood pressure correlate with weight status) and therefore the tests are not truly independent tests, (c) significance of difference between CFL groups in one or more baseline values constitutes a finding worthy of further investigation and interpretation, which (d) would be otherwise missed, simply due to the inflation of type II errors being the inevitable consequence of reducing type I error rate.

Bonferroni adjustments, however, were applied to the gender-stratified investigations of baseline differences. Gender stratification was deemed necessary to investigate whether the baseline difference in body weight between the adherent and non-adherent groups was attributable to the difference in the proportion of female participants. This fulfills the criterion of repeated testing of sub-samples without prior hypotheses that these samples should differ [270]. Hence, the *p*-value for accepting significance of differences between CFL groups at baseline was set to 0.025 based on Equation 6 with n=2 and p=0.05.

Hypothesis Testing

Table 3 presents the methods of statistical inference as they were applied to answering the study questions.

Continuous variables are presented as mean and standard deviation (SD) or geometric mean and factor between means for non-normal distributed data after log-transformation. Categorical variables are presented with frequency and the relative frequency. Analyses for differences between groups at baseline were performed using unpaired *t*-test and the Chi-square (χ^2) test for categorical data. Change from baseline to follow-up within groups were tested using paired *t*-test for continuous data, or the Chi-square test or Fischer's exact test for categorical data. Changes from baseline to follow-up were tested between CFL groups using the *t*-test for continuous data, and the Chi-square test for categorical data. Statistical significance was accepted at $p<0.05$.

Table 3:

Methods of Statistical Inference

	Type of Variable	Type of statistical problem	Method applied
Comparison of the means of baseline values between CFL+ & CFL- groups	Interval nominal	Two independent samples, one variable	Two-sample t-test Fisher's Exact Test
Proportion of CFL+ subjects in the sample population		Comparison with specified proportion	Test of Proportions
Change in parameters from baseline to follow-up within each CFL group	interval	One variable, two dependent samples	Paired t-test
Comparison of the mean changes from baseline to follow-up between CFL groups	interval	One variable, two independent samples	Two-sample t-test
Odds Ratio (OR)		One binomial variable, two independent samples	2x2 contingency table methods, $\chi 2$ test

The following parameters were assessed continuously, as the primary and secondary outcome variables of interest: VO_2peak, body weight, BMI, body fat, TCH, HDL, LDL, TG, BPsys, BPdia, PROCAM risk score. The lipid ratio TCH/HDL was also calculated and assessed continuously.

Ratio- and interval-type baseline and follow-up data were tested for normality of the distribution using skewness-kurtosis and Shapiro-Wilk tests.

All variables were visually inspected for normality using Q-Q Plots. In the case of Shapiro-Wilk tests and Q-Q plots suggesting violation of the normality assumption, attempts were made to normalize the distributions through suitable transformations. If successful, analyses were performed on transformed and natural data. This was done with a specific view to examining significance in all cases where the combination of medium or large effect sizes (between groups or within groups from baseline to follow-up) with the between- or within-group differences approaching, but not reaching, significance suggested insufficient power of the parametric analyses when performed on the untransformed data. Nonparametric tests were used when data were non-normally distributed and no suitable transformation for establishing normality could be found.

Independent samples t-tests were conducted as univariate analyses to compare the parameters at baseline between adherent and non-adherent subject groups (CFL+ and CFL- groups respectively, see definition under the section “adherence”). Within-group changes from baseline to follow-up were evaluated using paired t-tests. Between-group changes from baseline to follow-up were compared using t-tests assuming unequal variances wherever appropriate.

To evaluate whether the probability of modifying outcome parameters to a clinically relevant extent was significantly different between CFL groups, outcome parameters were first dichotomized along clinically relevant minimum values of change. Subsequently, two-by-two contingency tables were constructed to assess whether a change in parameter was related to CFL-group association. Significance of the relation was assessed using Chi-squared tests for all tables in which all expected cell frequencies exceeded 5. In cases of expected cell frequencies being <5, the results of Fisher’s exact tests were accepted to determine significance. In the case of significant findings, odds ratios were calculated and their 95% CI were assessed using logistic regression.

All tests were performed on raw and transformed data to determine whether the findings of significance derived from analyses of the raw data could be confirmed from the transformed data as well. If analyses performed on transformed data did not support the findings derived from analyses of raw data, null hypotheses of significance were accepted.

Tests for equality of variances were performed using a robust test originally suggested by Levene [271]. This test, found to be robust under non-normality and further improved by Brown and Forsythe [272], has been implemented as a test statistic in the statistical software STATA which was used to carry out all analyses (see below).

To determine whether findings of statistical significance translated into clinical relevance, the interval-type data for changes of VO2peak, total and HDL cholesterol, TCH/HDL ratio, body

fat percent and body weight (expressed as percent change) were first dichotomized along evidence-based demarcations for clinical relevance (clinical relevance defined as VO2peak change >= 3.5 ml/kg/min, body weight change >=5% of baseline weight, change of body fat, TCH and HDL >=10% respectively). Logistic regression was conducted to calculate odds ratios (ORs) and 95% CIs of these dichotomized variables associated with CFL group status in CFL strata (see following section).

Statistical significance was accepted with $P < 0.05$. Analyses were carried out with Intercooled STATA 11 for Macintosh (Stata Corp. Texas, U.S.A.) and all data are expressed as means ± 1SD unless noted otherwise.

DEFINING ADHERENCE – THE DETERMINANTS OF THE CONTROLLED FEEDBACK LOOP

Typically the degree of adherence to an intervention determines the cumulative intervention dose to which a subject will have exposed himself at the time of follow-up. This is an important aspect to consider when investigating the strength of the association between the intervention and its hypothesized outcome. In behavior modification interventions, this does not answer the question what proportion of individuals leaves the intervention with a suitably modified lifestyle behavior. For example, an 80% adherence rate to a physical activity curriculum may not be so impressive if the 20% non-adherence has been accumulated through consecutively missed sessions prior to the intervention end, suggesting non-sustainability of the curriculum. One of this trial's objectives is to answer the question whether and to which degree adherence to its curriculum has been sustained in free-living individuals by trial's end. It *a priori* accepts an association to exist between PA and health outcome (as discussed in the preceding sections). What it attempts to answer is whether the intervention strategy which is specifically aimed at making adherence to PA sustainable, will, at the time of follow-up, see a large enough proportion of participants acutely availing themselves to PA at a large enough dose and having done so over a long enough duration that the accrued measurable health benefits support subjecting this intervention to larger and longer-term prospective follow-up investigations upon its chronic public health benefits.

To put it simple: while preceding trials have established the effect of taking the medicine (PA), this trial begins to investigate how to make people keep taking it.

Lack of time is the most frequently cited obstacle to the cultivation of a regular exercise habit [273-275]. Whether real or imagined, this concern needs to be resolved if the high prevalence of sedentism and its associated diseases are to be substantially reduced [276].

It is conceivable that the conflict between time available and time required for exercise freezes an individual into a sedentary lifestyle. The current exercise recommendations may inadvertently promote this conflict. In its 2009 position statement, the ACSM states that 150-250 minutes of moderate-intensity exercise per week may just be sufficient to prevent weight gain, whereas PA in excess of 250 minutes is required to achieve clinically significant weight losses in overweight and obese persons [277]. The Institute of Medicine advocates at least 60 minutes of moderate physical activity 7 days per week [278].

To many currently sedentary individuals these recommendations are in conflict with their real or imagined time constraints.

Recent research has shown that clinically relevant health benefits accrue from exercise of shorter duration but higher intensity, which may more easily fit into individuals' time budgets [279, 280]. Specifically high intensity interval training (HIT) has emerged as astonishingly effective in relatively small doses. HIT typically consists of sequences of high intensity training, such as running or cycling at or above 80% of VO2max or near maximal heart rate

for 1 to 4 minutes, followed by a period of active recovery, such as running or cycling at or above the anaerobic threshold.

Insulin action and glucose metabolism appear to markedly benefit from such routines [281]. One potential reason for this effect is that while type-1 (fast-twitch) muscle fibers replenish their glycogen stores during recovery, regardless of the type of recovery, type-2 (slow-twitch oxygenating) fibers continue to deplete their glycogen stores, but only during active and not during passive recovery [282].

HIT also improves fitness and the metabolic syndrome substantially better than continuous moderate exercise [283]. Even for chronic heart failure patients, HIT has emerged as an effective medicine for improving cardiac function, quality of life (QoL) and survival [284, 285].

With respect to endothelial function, moderate intensity exercise my be insufficient to elicit an anti-inflammatory response [286], whereas HIT exerts a strong protective effect against endothelial dysfunction resulting from post-prandial lipemia [287].

With thrice weekly 15-minute HIT bouts yielding significant improvements of parameters of metabolism and exercise capacity [281], I defined as minimum PA volume for this trial a thrice weekly 20-minute HIT routine consisting of 4 one-minute all-out PA periods each followed by a 4-minute active recovery period of moderate-to-high-intensity PA to be performed consecutively on alternating weekdays. Hence, 60 weekly minutes of exercise performed in HIT mode constituted the minimum requirement for exercise volume in this trial. This is also in line with U.S. government recommendations, published under the “Healthy People 2010” initiative, and calling for moderate intensity exercise of at least 30 minutes on at least 5 days per week, or alternatively, for 20 minutes high intensity exercise at least thrice weekly [288].

I rationalized that even if no measurable benefits would accrue over the trial period, participants would probably find it relatively easy to establish a PA routine based on these minimal time requirements from which a subsequent increase in weekly exercise volume would be perceived as less demanding, than to begin with a larger volume right from the start. I therefore designed the protocol to be minimally invasive with respect to subjects’ perceived time constraints while at the same time capable of producing clinically relevant health benefits as suggested by published evidence.

Hence, adherence (having an operant cognitive controlled feedback loop) was defined as meeting or exceeding the minimum requirements of having performed the 60-minutes weekly volume of HIT for at least 12 consecutive weeks, with the last recorded entry into the self-monitoring tool having occurred not longer than 7 days prior to the follow-up assessment. Subjects are henceforth dichotomized into CFL+ (adherent, based on the aforementioned criteria) and CFL- groups. With physical fitness being the primary and measurable health outcome, the 12 weeks duration is in keeping with published evidence, which suggests that measurable effects accrue to VO2max after such durations [106] with decay of the effect being observable within 14 days of discontinuation of the exercise regimen [289].

DESCRIPTION OF THE PHYSICAL ACTIVITY INTERVENTION

All participants received a detailed personal appraisal of their baseline measurement results by the author. A standardized summary of the results with explanations of how to interpret them was made available for download from the web-based electronic lifestyle file (ELF) for each participant (see attachment). Participants were then familiarized with the use of their web based electronic lifestyle file for monitoring and logging their PA data (see attachment). A minimum PA curriculum of thrice weekly 20 continuous minutes of HIT was agreed to by all participants, with recommendations given for aerobic and/or resistance exercise to be performed in excess of this minimum requirement. These recommendations were based on each participant's health profile with a view to improving specific health parameters. The mode of exercise to be performed was left to the participants in accordance with their preferences and abilities. Jogging (as distinct from walking) was the type of activity preferred by most participants, followed by cycling or a combination of both exercise types. Only two participants chose swimming as the primary mode of exercise, both of these participants however, emerged among the CFL- group.

All participants who opted for the use of heart rate monitors during exercise were given target heart rates for the HIT exercises and recommendations for the optimal heart rates during continuous aerobic exercise based on their individual CEPT results. Participants who decided against the use of heart rate monitors were familiarized with the use of the 10-point OMNI rating scale of perceived exertion [290] (translated into the German language by the author) and instructed to perform the high-intensity intervals at an approximate rating of 8 and the recovery phase at a rating of 5-6 (see appendix). The OMNI scale has been validated for use in equivalent populations [291, 292].

Exercise Curriculum

The common denominator for all participants was a high intensity interval (HIT) protocol of thrice weekly 20 minutes of interval exercise (either running or cycling). Each 20-minute session consisted of 4 repeated 60-s sprints at a heart rate commensurate with 85% to 95% of participants' individual VO2max (as assessed for each participant at baseline) with a 4-min recovery phase between sprints. During recovery, subjects were to continue their mode of exercise at an intensity level commensurate with their anaerobic threshold. Subjects were instructed not to perform HIT on consecutive days, but were encouraged to engage in other exercise, such as resistance training or moderate intensity endurance training at 95-115% of their individual anaerobic threshold. The exercise volume to which a participant had agreed during the individual appraisal session was expressed in a simple point system, in which 1 point reflected 5 minutes of exercise. The ELF facilitates a 6-weeks cumulative graphical display of actual vs. target performance. Thus a point score of 72 reflects the minimum curriculum of thrice weekly 20-minutes of HIT. Target point scores for the initial 6-weeks

period were based on the PA volume which each participant voluntarily agreed to perform. Participants were encouraged to log their actual PA performance on an as-and-when-performed basis, either by direct access to their secured web-page or through an applet installed on their mobile phone facilitating SMS-based reporting of point scores.

Monitored Self-Monitoring

Participants were informed that the author/investigator continuously monitors each participant's self-reported progress and that (a) failure to report progress for more than 7 consecutive days, or (b) foreseeable failure to achieve the target point score will prompt the investigator to contact the participant personally (via phone or email) to enquire about the reasons. Verbal agreement to this procedure had been obtained by the author from all participants during the initial appraisal session.

Automated alarm features of the ELF (described in the attachment) provide for forecasting of actual progress vs. target progress and the definition of a variance which will trigger the alarm. Alarms trigger the sending of email, fax or SMS to operator-defined recipients (in this case, the author) to inform about the fact and type of triggering event.

After the completion of each 6-weeks period, the ELF automatically issues a new training plan adjusting the target point-scores based on self-reported results achieved during the completed cycle (see attachment). The automatically issued training targets are increased over the previously achieved actual score by a fixed percentage, so as to motivate the participants to increase their exercise curriculum up to a pre-set maximum of 60 minutes per day.

There was no monitoring of actual intensity at which participants performed the HIT sessions. However, participants were encouraged to contact the author/investigator in case of any questions or doubts pertaining to the exercise routines or other aspects of the intervention program.

Active self-monitoring was defined as meeting all three of the following conditions:

- ***latency:*** 7 days or less between last logged PA and follow-up examination
- ***duration:*** 90 consecutive days of continuous weekly self-monitoring
- ***volume:*** 60 minutes of weekly volume of recorded exercise

RESULTS

Of the 117 participants enrolled into this study 89 individuals met all three criteria for being actively self-monitoring at follow-up (CFL+), thereby qualifying as adherent. Of these 89 CFL^+ subjects 8 individuals performed self-monitoring off-line using manual record books. Reasons given for not using the internet tool were

- having no or only occasional internet access (5 subjects)
- being inconvenienced by internet recording (3 subjects)

The manual PA logs of all 8 offline self-monitoring subjects were verifiable against attendance records in the on-site fitness center at which most subjects performed their PA sessions.

Of the 28 subjects who did not meet the CFL+ requirements (CFL^- participants, or non-adherent), 5 subjects had sustained injuries (unrelated to the intervention protocol), which had prevented them from continuing their PA curriculum.

One subject felt unable to maintain a regular exercise schedule, owing to a new assignment, which required extended and frequent overseas' business trips.

Of the remaining 22 subjects

- 5 subjects (4 males) had exceeded the volume and duration requirements but had failed to meet the latency requirement due to their discontinuation of self-monitoring of physical activity between 9 to 20 days prior to the follow-up assessment. The reason given by all 5 subjects was their confidence in their ability to maintain the newly acquired PA habit without any further need to record it.
- 15 subjects had displayed an "on-off" adherence and did not meet the volume, duration and latency criteria to various degrees.
- 2 male participants did not meet any of the latency, volume and duration requirements and failed to attend the follow-up assessments. Both participants had expressed a loss of interest in the program as the reason for discontinuation.

Adherence Stratification

To facilitate analyses of the associations between intervention duration and intervention effects, CFL status was dichotomized into three strata CFL90, CFL120 and CFL 150, with the only inter-category difference being the duration of recorded self-monitoring (90 days, 120 days and 150 days respectively). The latency and volume aspects of the adherence definition remained the same for all three strata, with 7 days or less between last logged PA and follow-up examination, and a minimum of 60 weekly minutes of reported PA.

DATA ACQUISITION

Availability of valid data for statistical analyses by adherence status and by CFL strata is presented in Figure 4.

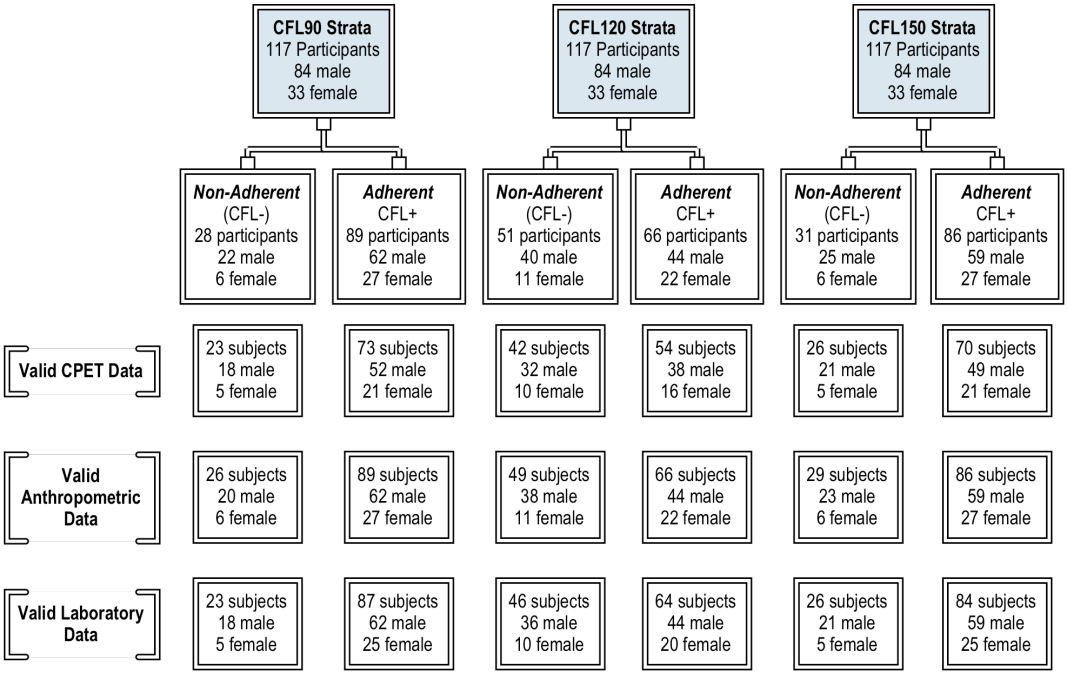

Figure 4. **Data availability for ELF participants by CFL (adherence) status by CFL Strata.**

Cardiopulmonary Exercise Testing (CPET)

Ergospirometric exercise tests had been performed on all 117 subjects at baseline and for 115 subjects at follow-up (2 CFL^- - subjects had failed to participate in the follow-up evaluations). For 19 subjects (3 CFL^- participants and 16 CFL^+ participants) one or both of the tests had to be terminated prematurely due to blood pressure excursions (7 subjects), musculoskeletal complaints (11 subjects) or both (1 subject). As a result, the complete ergospirometric data (baseline and follow-up) of 23 CFL^- subjects and 73 CFL^+ subjects were available for statistical evaluation to test hypothesis 2a.

Body Composition And Weight Status

Body weight data from baseline and follow-up assessment were available for 115 subjects. Follow-up data were missing for the 2 subjects who had failed to participate in the follow-up assessment.

Laboratory Analyses

Complete data for blood cholesterol and lipid values were available for 23 CFL^- subjects and 87 CFL^+ subjects. 5 CFL^- subjects had refused participation in the sampling of blood at follow-

up. One CFL^+ subject had refused participation in the sampling of blood at baseline and follow-up, and for one CFL^+ subject the baseline data had to be ignored due to self-reported violation of the fasting requirement prior to blood sampling.

COMPARISONS AT BASELINE

Table 4a presents the baseline values by adherence strata.

Table 4a:

Baseline Values By Adherence Strata

	CFL90[a]		CFL120[a]		CFL150[a]		
status[b]	non-adherent (N=28)	adherent (N=89)	non-adherent (N=31)	adherent (N=86)	non-adherent (N=51)	adherent (N=66)	total (N=117)
proportion[c] %	23.9 (16.1 to 31.8)	76.1 (68.2 to 83.9)	26.5 (18.4 to 34.6)	73.5 (65.4 to 81.6)	43.6 (34.5 to 52.7)	56.4 (47.3 to 65.5)	100
female[c] %	21.4 (5.8 to 37)	30.3 (20.6 to 40)	19.3 (5.1 to 33.6)	31.4 (21.4 to 41.4)	21.6 (10 to 33.1)	33.3 (21.7 to 44.9)	28.2 (19.9 – 36.4)
age	48.3 ±7.6	50.5 ±9.7	49 ±7.5	50.3 ±9.8	50.5 ±9.6	49.5 ±9	50 ±9.3
weight	93 ±13.6	86.7 ±15.1	93.4 ±13.7	86.4 ±15	90.8 ±14.7	86.3 ±14.9	88.2 ±14.9
BMI	29.8 ±4.5	28.6 ±4.1	29.9 ±4.4	28.6 ±4.1	29.2 ±4.3	28.7 ±4.1	28.9 ±4.2
%body fat	28.7 ±8.2	28.9 ±7.5	28.6 ±8.1	29 ±7.5	28.3 ±8.4	29.3 ±7.1	28.9 ±7.7
VO2peak	31.8 ±7.8	32 ±8.2	31.8 ±7.7	32 ±8.2	31.3 ±8.5	32.5 ±7.7	32 ±8
TCH	221.3 ±54.6	224 ±49.2	221 ±52	224.2 ±50	225.2 ±54.7	221.9 ±46.9	223.4 ±50.3
HDL	55.2 ±16.4	54.5 ±13	54.4 ±15.9	54.8 ±13.1	55.6 ±14	54 ±13.8	54.7 ±13.8
LDL	137.4 ±47.5	138.5 ±44.6	136.2 ±45.5	139 ±45.2	138.4 ±45.6	138.1 ±45.1	138.2 ±45.1
TCH/HDL	4.3 ±1.2	4.3 ±1.2	4.3 ±1.2	4.3 ±1.2	4.3 ±1.2	4.3 ±1.2	4.3 ±1.2
TG	143.7 ±71.7	155.3 ±104.9	151.7 ±81.2	152.8 ±103.5	156.5 ±117.5	149.3 ±79.2	152.5 ±97.7
BPsys	136.1 ±12	142.6 ±16.3	136.8 ±12	142.5 ±16.5	138.8 ±12.9	142.7 ±17.3	141 ±15.6
BPdia	82.9 ±8.5	82.8 ±10	83.3 ±8.3	82.6 ±10.1	81.3 ±10.4	84.1 ±8.8	82.8 ±9.6
PROCAM	3.8 ±4.7	5.2 ±6.6	4.6 ±5.8	4.9 ±6.4	5.4 ±7.9	4.4 ±4.4	4.9 ±6.2

Note: Data are means ± SD unless otherwise noted.
TCH: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; VO2peak: peak oxygen consumption: BMI: body mass index (kg/m^2) BPsys: systolic blood pressure (mmHg); BPdia: diastolic blood pressure (mmHg); PROCAM: PROCAM risk score;
a - CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
b – values in brackets: numbers of subjects
c - values in brackets: 95% confidence interval

To test the hypothesis of no significant baseline differences between active and inactive groups within each adherence strata, independent-samples t tests were conducted on all variables. Independent-samples t tests are based on the assumptions of a normally distributed variable and equal variances of the variables for the populations under comparison. Therefore all test variables were inspected for normality using Shapiro-Wilk tests and Q-Q plots. In case of violations of the assumption of normality (age, triglycerides, PROCAM score) suitable transformations were performed to create a more normally

distributed variable. Levene's tests for equal variances were subsequently performed on the raw and transformed variables, following which, t-tests were conducted on the raw and transformed variables, assuming unequal variance in all cases where the assumption of equality of variance was found to be violated (triglycerides only). Results of the t-tests (performed on the untransformed raw variable data, except for PROCAM score) are presented in Tables 4b-d and explained thereafter.

Table 4b:

CFL90 Strata Baseline Values by CFL Group

		CFL- N_{male}=22 N_{female}=6	CFL+ N_{male}=62 N_{female}=27	Δ	significance	Pooled SD	Effect Size (Cohen's d)
Gender (95% CI)	Female (%)	21.4 % 6.2 to 36.6	30.3 % 20.7 to 39.8	8.9	z=-0.91, *p*=0.36		
Age	Male	49.3 ±7.6	51.2 ±8.1	1.9	t(39.4)=-0.97, *p*=0.33	7.88	0.24
	Female	44.3 ±6.37	48.6 ±12.37	4.3	t(14.8)=-1.2, *p*=0.24	11.2	0.38
	total	48.3 ±7.6	50.4 ±9.6	2.1	t(115)=-1.08, *p*=0.28	9.09	0.23
Weight kg	Male	93.3 ±12.4	90.6 ±13.7	-2.7	t(82)=0.82, *p*=0.41	13.2	0.2
	Female	91.7 ±18.5	77.7 ±14.1	-14	t(31)=2.07, *p*=0.04	14.4	0.9
	total	93.0 ±13.6	86.7 ±15.0	-6.3	t(115)=-1.98, *p*=0.05	14.5	0.43
BMI kg/m^2	Male	28.8 ±3.1	28.6 ±3.7	-0.2	t(82)=0.16, *p*=0.87	3.5	0.05
	Female	33.4 ±6.7	28.4 ±4.6	-5	t(31)=2.17, *p*=0.03	4.8	1.0
	total	29.8 ±4.4	28.6 ±4.0	-1.2	t(115)=-1.34, *p*=0.18	4.0	0.29
%Body fat	Male	25.3 ±4.4	25.5 ±5.0	0.2	t(82)=-0.21, *p*=0.82	4.8	0.04
	Female	41.1 ±6.3	36.5 ±6.5	-4.6	t(31)=1.59, *p*=0.12	6.3	0.7
	total	28.7 ±8.2	28.9 ±7.5	0.2	t(115)=-0.11, *p*=0.91	7.6	0.03
VO2peak ml/kg/min	Male	34.2 ±6.4	34.7 ±7.4	0.5	t(82)=-0.27, *p*=0.78	7.1	0.07
	Female	22.6 ±4.3	25.6 ±5.4	3.0	t(31)=-1.23, *p*=0.22	5.1	0.59
	total	31.8 ±7.7	32.0 ±8.1	0.2	t(115)=-0.12, *p*=0.90	7.9	0.02
HDL[a] mg/dL	Male	52.4 ±14.9	50.2 ±9.1	-2.2	t(82)=0.82, *p*=0.4	10.7	0.2
	Female[1]	65.3 ±18.5	65.1 ±15.0	-0.2	t(29)=0.02, *p*=0.97	15.1	0.01
	total	55.2 ±16.3	54.5 ±13.0	-0.7	t(113)=0.23, *p*=0.81	13.7	0.05
TCh[a] mg/dL	Male	219 ±58	226 ±50	7	t(82)=-0.51, *p*=0.6	51.5	0.1
	Female	229 ±41	219 ±48	-10	t(29)=0.44, *p*=0.66	45	0.22
	total	221.2 ±54.5	224.0 ±49.1	2.8	t(113)=-0.25, *p*=0.80	50.0	0.05
LDL[a] mg/dL	Male	136 ±51	142 ±44	6	t(82)=-0.51, *p*=0.6	45.3	0.1
	Female	140 ±35	129 ±44	-11	t(29)=0.59, *p*=0.55	41.2	0.26
	total	137.3 ±47.5	138.5 ±44.6	1.2	t(113)=-0.11, *p*=0.90	44.9	0.03
TCh/HDL[a] ratio	Male	4.3 ±1.0	4.5 ±1.0	0.2	t(82)=-0.91, *p*=0.36	0.99	0.2
	Female[1]	3.8 ±1.3	3.5 ±0.9	-0.3	t(29)=0.61, *p*=0.54	0.95	0.31
	total	4.2 ±1.2	4.3 ±1.2	0.1	t(113)=-0.21, *p*=0.83	1.19	0.08
TG[a]	Male	151 ±77	166 ±116	15	t(56.3)=-0.69, *p*=0.49	106	0.1
	Female	116 ±42	127 ±61	11	t(10.7)=-0.54, *p*=0.59	56.3	0.19
	total	143.6 ±71.7	155.3 ±104.8	11.7	t(66.9)=-0.66, *p*=0.51	97.2	0.12
BPsys[b]	Male	136 ±12	144 ±16	8	t(79)=-2.03, *p*=0.05	14.9	0.5
	Female	137 ±12	140 ±17	3	t(27)=-0.4, *p*=0.69	15.8	0.18
	total	136 ±12	143 ±16	7	t(108)=-1.89, *p*=0.06	15	0.46
BPdia[b]	Male	83 ±9	85 ±9	2	t(79)=-0.83, *p*=0.4	8.9	0.22
	Female	84 ±7	78 ±11	-6	t(27)=1.04, *p*=0.3	10.1	0.59
	total	83 ±8	83 ±10	0	t(108)=0.06, *p*=0.95	9.5	0
PROCAM[c]	Male N=22/58	2.81 (1.7 to 4.65)	4.7 (3.73 to 5.93)	1.67	t(78)=2.15, *p*=0.03		
	Female N=5/23	0.03 (0 to 0.1)	0.04 (0 to 0.1)	1.5	t(26)=0.46, *p*=0.6		
	total	1.19 (0.51 to 2.77)	1.22 (0.7 to 2.13)	1.03	t(106)=0.05, *p*=0.9		

Note: Data are means ± SD unless otherwise noted.
TCH: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; VO2peak: peak oxygen consumption; BMI: body mass index (kg/m^2) BPsys: systolic blood pressure (mmHg); BPdia: diastolic blood pressure (mmHg); PROCAM: PROCAM risk score;
a: number of female participants for whom blood analysis data were available: 31
b: 81 male and 29 female participants for whom valid blood pressure data were available
c: means are geometric means, and Δ is the factor between means (after antilog of the log-transformed data); values in brackets are 95% CI

Table 4c:

CFL120 Strata Baseline Values by CFL Group

		CFL- N_{male}=25 N_{female}=6	CFL+ N_{male}=59 N_{female}=27	Δ	significance	Pooled SD	Effect Size (Cohen's d)
Age	Male	50.1 ±7.4	51 ±8.3	0.9	t(50.4)=-0.51, *p*=0.6	7.9	0.11
	Female	44.3 ±6.37	48.6 ±12.37	4.3	t(14.8)=-1.2, *p*=0.24	11.2	0.38
	total	49.0 ±7.5	50.3 ±9.8	1.3	t(68.8)=-0.76, *p*=0.44	9.2	0.14
Weight kg	Male	93.7 ±12.6	90.3 ±13.6	-3.4	t(82)=1.07, *p*=0.28	13.1	0.25
	Female	91.7 ±18.5	77.7 ±14.1	-14	t(31)=2.07, *p*=0.04	14.4	0.9
	total	93.3 ±13.6	86.3 ±14.9	7	t(115)=2.28, *p*=0.02	14.4	0.48
BMI kg/m^2	Male	29.0 ±3.2	28.5 ±3.7	-0.5	t(82)=0.57, *p*=0.56	3.5	0.1
	Female	33.4 ±6.7	28.4 ±4.6	-5	t(31)=2.17, *p*=0.03	4.8	1.0
	total	29.9 ±4.4	28.5 ±4.0	1.4	t(115)=1.58, *p*=0.11	4.07	0.34
%Body fat	Male	25.5 ±4.7	25.5 ±4.9	0	t(82)=-0.017, *p*=0.98	4.8	0
	Female	41.1 ±6.3	36.5 ±6.5	-4.6	t(31)=1.59, *p*=0.12	6.3	0.7
	total	28.5 ±8.0	28.9 ±7.5	0.4	t(115)=-0.27, *p*=0.78	7.6	0.05
VO2peak ml/kg/min	Male	33.9 ±6.6	34.9 ±7.5	1.0	t(82)=-0.54, *p*=0.58	7.1	0.1
	Female	22.6 ±4.3	25.6 ±5.4	3.0	t(31)=-1.23, *p*=0.22	5.1	0.59
	total	31.8 ±7.7	32.0 ±8.1	0.2	t(115)=-0.12, *p*=0.89	7.9	0.02
HDL[a] mg/dL	Male	51.7 ±14.3	50.3 ±9.2	-1.4	t(82)=0.55, *p*=0.58	10.8	0.1
	Female	65.3 ±18.5	65.1 ±15.0	-0.2	t(29)=0.02, *p*=0.97	15.1	0.01
	total	54.4 ±15.8	54.7 ±13.1	0.3	t(113)=-0.11, *p*=0.90	13.7	0.02
TCh[a] mg/dL	Male	219 ±54.8	226.2 ±51	7.2	t(82)=-0.58, *p*=0.56	45.5	0.15
	Female	229 ±41	219 ±48	-10	t(29)=0.44, *p*=0.66	45	0.22
	total	220.9 ±51.9	224.2 ±49.9	3.3	t(113)=-0.31, *p*=0.75	50	0.06
LDL[a] mg/dL	Male	135 ±48	143 ±45	8	t(82)=-0.72, *p*=0.47	45.3	0.17
	Female	140 ±35	129 ±44	-11	t(29)=0.59, *p*=0.55	41.2	0.26
	total	136.2 ±45.5	138.9 ±45.2	2.7	t(113)=-0.28, *p*=0.77	44.8	0.06
TCh/HDL[a] ratio	Male	4.4 ±1.1	4.6 ±1.1	0.2	t(82)=-0.74, *p*=0.46	1.08	0.18
	Female	3.8 ±1.3	3.5 ±0.9	-0.3	t(29)=0.61, *p*=0.54	0.95	0.31
	total	4.3 ±1.1	4.3 ±1.2	0.0	t(113)=-0.05, *p*=0.95	1.16	0.0
TG[a]	Male	160.2 ±86.4	163.5 ±115.6	3.3	t(82)=0.14, *p*=0.88	106.5	0.03
	Female	116 ±42	127 ±61	11	t(10.7)=-0.54, *p*=0.59	56.3	0.19
	total	151.6 ±81.2	152.7 ±103.5	1.1	t(66.9)=-0.05, *p*=0.95	97.2	0.01
BPsys[b]	Male	137 ±12	144 ±16	7	t(79)=-1.85, *p*=0.06	14.7	0.47
	Female	137 ±13	140 ±17	3	t(27)=-0.4, *p*=0.69	15.9	0.18
	total	137 ±12	142 ±16	5	t(108)=-1.72, *p*=0.08	14.9	0.33
BPdia[b]	Male	83 ±9	85 ±9	2	t(79)=-0.56, *p*=0.57	8.9	0.22
	Female	84 ±7	78 ±11	-6	t(27)=1.04, *p*=0.3	10.1	0.59
	total	83 ±8	83 ±10	0	t(108)=0.33, *p*=0.73	9.4	0.0
PROCAM[c]	Male N=25/55	3.22 (2.01 to 5.2)	4.52 (3.56 to 5.7)	1.39	t(78)=1.41, *p*=0.16		
	Female N=5/23	0.02 (0 to 0.1)	0.04 (0 to 0.1)	1.53	t(26)=0.46, *p*=0.6		
	total N=30/78	1.46 (0.66 to 3.22)	1.12 (0.65 to 2.0)	1.28	t(106)=0.49, *p*=0.6		

Note: Data are means ± SD unless otherwise noted.
TCH: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; VO2peak: peak oxygen consumption; BMI: body mass index (kg/m^2) BPsys: systolic blood pressure (mmHg); BPdia: diastolic blood pressure (mmHg); PROCAM: PROCAM risk score;

a: number of female participants for whom blood analysis data were available: 31
b: 81 male and 29 female participants for whom valid blood pressure data were available
c: means are geometric means, and Δ is the factor between means (after antilog of the log-transformed data); values in brackets are 95% CI

Table 4d:

CFL150 Strata Baseline Values by CFL Group

		CFL- N_{male}=40 N_{female}=11	CFL+ N_{male}=44 N_{female}=22	Δ	significance	Pooled SD	Effect Size (Cohen's d)
Age	Male	50.3 ±9.4	51.1 ±6.6	0.8	t(69.2)=-0.42, *p*=0.6	7.9	0.1
	Female	51 ±10.5	46.3 ±11.9	-4.7	t(22.4)=1.15, *p*=0.25	11.1	0.4
	total	50.5 ± 9.6	49.5 ±9.0	1.0	t(115)=0.57, *p*=0.56	9.2	0.1
Weight kg	Male	91.7 ±13.8	90.8 ±13.1	-0.9	t(82)=0.29, *p*=0.7	13.2	0.06
	Female	86.9 ±17.5	76.9 ±13.9	-10	t(31)=1.79, *p*=0.08	14.6	0.68
	total	90.7 ±14.7	86.2 ±14.9	4.5	t(115)=1.63, *p*=0.1	14.6	0.3
BMI kg/m^2	Male	28.5 ±3.5	28.9 ±3.6	0.4	t(82)=-0.55, *p*=0.57	3.5	0.11
	Female	31.4 ±5.9	28.2 ±4.8	-3.2	t(31)=1.66, *p*=0.1	5.0	0.6
	total	29.1 ±4.3	28.7 ±4.1	0.4	t(115)=0.54, *p*=0.58	4.2	0.09
%Body fat	Male	25 ±5.3	25.9 ±4.3	0.9	t(82)=0.88, *p*=0.37	4.7	0.18
	Female	40.1 ±6.2	35.9 ±6.5	6.5	t(31)=1.76, *p*=0.08	6.2	0.67
	total	28.3 ±8.3	29.3 ±7.0	1.0%	t(115)=-0.71, *p*=0.47	7.5	0.13
VO2peak ml/kg/min	Male	33.5 ±7.7	35.6 ±6.6	2.1	t(82)=-1.35, *p*=0.17	7.0	0.29
	Female	23 ±5.0	26 ±5.3	3.0	t(31)=-1.59, *p*=0.11	5.0	0.59
	total	31.2 ±8.4	32.5 ±7.7	1.3	t(115)=-0.81, *p*=0.41	7.9	0.16
HDL[a] mg/dL	Male	52.9 ±12.8	48.8 ±8.4	4.1	t(82)=1.74, *p*=0.08	10.5	0.38
	Female	65.0 ±14.1	65.2 ±16.4	0.2	t(29)=-0.04, *p*=0.96	15.1	0.01
	total	55.5 ±13.9	53.9 ±13.8	1.6	t(113)=-0.6, *p*=0.54	13.7	0.11
TCh[a] mg/dL	Male	225.8 ±58	222.4 ±46.3	-3.4	t(82)=0.3, *p*=0.76	51.5	0.06
	Female	222.3 ±42	220.6 ±49.2	-1.7	t(29)=0.1, *p*=0.92	45	0.03
	total	225.1 ±54.6	221.9 ±46.9	3.2	t(113)=-0.34, *p*=0.73	50.0	0.06
LDL[a] mg/dL	Male	139.1 ±48.3	142.3 ±44.3	3.2	t(82)=-0.32, *p*=0.74	45.6	0.07
	Female	135.5 ±35.4	128.6 ±46.2	-6.9	t(29)=0.42, *p*=0.67	41.3	0.16
	total	138.3 ±45.6	138.1 ±45.1	0.2	t(113)=-0.02, *p*=0.97	44.9	0.004
TCh/HDL[a] ratio	Male	4.4 ±1.16	4.6 ±1.01	0.2	t(82)=-1.01, *p*=0.31	1.07	0.18
	Female	3.5 ±1.03	3.5 ±1.0	0.0	t(29)=0.09 *p*=0.92	0.97	0.0
	total	4.2 ±1.2	4.3 ±1.1	0.1	t(113)=-0.34, *p*=0.73	1.1	0.08
TG[a]	Male	169.4 ±128.7	156.3 ±84.2	-13.1	t(82)=0.55, *p*=0.57	106.3	0.12
	Female	109.2 ±35.7	133.5 ±65.7	24.3	t(29)=-1.1, *p*=0.26	55.2	0.43
	total	156.5 ±117.5	149.2 ±79.1	7.3	t(83.9)=-0.37, *p*=0.7	97.1	0.07
BPsys[b]	Male	139 ±13	144 ±17	5	t(79)=-1.29, *p*=0.2	15	0.33
	Female	137 ±14	141 ±18	4	t(27)=-0.5, *p*=0.59	16.3	0.24
	total	139 ±13	143 ±17	4	t(108)=-1.31, *p*=0.19	15.2	0.26
BPdia[b]	Male	83 ±10	85 ±8	2	t(79)=-1.43, *p*=0.15	8.9	0.22
	Female	76 ±11	81 ±10	5	t(27)=-1.23, *p*=0.2	10	0.49
	total	81 ±10	84 ±9	3	t(108)=-1.52, *p*=0.12	9.4	0.32
PROCAM[c]	Male N=38/42	3.49 (2.41 to 5.05)	4.66 (3.63 to 5.98)	1.33	t(78)=1.33, *p*=0.18		
	Female N=10/18	0.05 (0.02 to 0.14)	0.03 (0 to 0.08)	0.6	t(26)=0.79, *p*=0.4		
	total N=48/60	1.47 (0.81 to 2.66)	1.04 (1.89 to 2.05)	0.68	t(106)=0.74, *p*=0.45		

Note: Data are means ± SD unless otherwise noted.
TCH: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; VO2peak: peak oxygen consumption; BMI: body mass index (kg/m^2) BPsys: systolic blood pressure (mmHg); BPdia: diastolic blood pressure (mmHg); PROCAM: PROCAM risk score;
a: number of female participants for whom blood analysis data were available: 31
b: 81 male and 29 female participants for whom valid blood pressure data were available
c: means are geometric means, and Δ is the factor between means (after antilog of the log-transformed data); values in brackets are 95% CI

Between-group differences in each strata were non significant, with the exception of body weight and BMI approaching significance among females in the CFL90 and CFL120 strata.

Gender

The proportion of females was not significantly different between the CFL groups of each CFL strata. In the CFL90 strata the proportions were 21.4% (95% CI 6.2 to 36.6) and 30.3% (95% CI 20.7 to 39.8) for the CFL- and CFL+ groups respectively, with z=-0.91, p=0.36. In the CFL120 strata the proportions were 19.3% (95% CI 5.4 to 33.2) and 31.4% (95% CI 21.5 to 41.2) for the CFL- and CFL+ groups respectively, with z=-1.27, p=0.2. In the CFL150 strata the proportions were 21.5% (95% CI 10.2 to 32.8) and 33.3% (95% CI 21.9 to 44.7) for the CFL- and CFL+ groups respectively, with z=-1.4, p=0.16.

Age

While the CFL+ groups tended to be older than the CFL-groups the difference remained non-significant. In an attempt to normalize the distribution, age was log and square transformed and t-tests were repeated on each transformation. The between-group differences remained non-significant for the total as well as for the gender-specific subgroups.

Body Weight

Log-transformation achieved distributions to be not different from normal for all sub-groups.

t-tests performed on the log-transformed data confirmed the finding of p=0.04 of the between-group difference for females, with t(31)02.07 *p*=0.046. The between-group difference for the total mixed gender CFL groups became borderline significant with t(115)=2.06, p=0.0416.

Owing to the small sample sizes it is difficult to refute the hypothesis that body weight at baseline is a determinant for intervention adherence to a PA protocol.

If so, it is reasonable to assume that the degree of overweight, rather than absolute weight itself, might correlate with adherence to a PA intervention.

BMI

Between-group difference of BMI for the male subjects was small (0.2) and not significant, whereas the difference was large and significant in the female subgroup with a difference between means of 5 (33.4 vs. 28.4 in the CFL- and CFL+ groups respectively) and p<0.05.

However, one of the 6 female CFL- participants belonged to the group of 5 physically active subjects at follow-up who had failed to meet the latency requirement, but who had reported continued PA. This female participant had entered the study with a BMI of 39. To test the influence of this subject's values on the baseline comparison, t-test for significance of difference was performed with the data of this subject being reclassified into the female CFL+ group. Under these conditions the difference in BMI means was reduced to 3.56 between female CFL groups at baseline, and became non-significant with *t(31)=1.35, p=0.18*.

These observations suggest that if overweight status at baseline positively correlates with, or is a determinant of adherence to a PA intervention, the ELF sample may not have contained a sufficient number of individuals with a BMI in excess of the demarcation line, which separates the adherent from the non-adherent groups.

Body Fat

As with BMI, differences in percent body fat were small and not significant in the male subgroup as well in the total mixed-gender group, with a relatively large, but non-significant difference between the female subgroups. The latter remained non-significant after log and square-root transformations.

VO_2peak

There were no significant differences between groups at baseline. The moderate difference between the female groups is not significant.

Blood Lipids

There were no significant differences between CFL groups.

Blood Pressure

The male-only CFL+ group had a higher systolic blood pressure at baseline than the CFL- group (144 vs. 136 mmHg) which approached significance. Log transformation did not change the significance level with $t(79)=2.02$, $p=0.0465$. The difference in mean systolic pressure between the mixed gender groups also remained approaching, but not reaching significance, with $t(108)=1.86$, $p=0.065$ for the log-transformed data.

PROCAM Score

The risk score for both mixed-gender CFL groups remained well below the 10% cut-off, which is used to arbitrarily dichotomize between low and elevated risk categories. Due to the substantial deviation of the distribution from normality, PROCAM risk scores were log transformed, after which Shapiro-Wilk tests suggested normality of the distributions for the gender-specific sub-groups. Visual inspection of the histograms and Q-Q plots confirmed that, while the distributions were less skewed and closer to normality after log-transformation, deviation from normality was still considerable. Independent samples t-tests performed on the log-transformed values of the male subgroups approached significance (after consideration of the Bonferroni correction) for the difference between the two male CFL groups. Anti-log of the log transformed test results produces the geometric means (antilog of the means), the ratio of the geometric means (antilog of the difference between the means) and the confidence intervals for this ratio (antilog of the CI of the difference). For the male subgroups of the CFL90 strata the difference between geometric means of 2.8 and 4.7 for the CFL- and CFL+ groups respectively approached significance, with the $t(78)=-2.15$, $p=0.034$ two-tailed, indicating a ratio of 1.7 for the mean PROCAM risk scores between CFL groups. For the CFL120 and CFL150 strata no significance of difference was observed, neither for the comparisons of gender-specific subgroups nor of the mixed-gender groups.

Comparison with the underlying population

With the given recruitment strategy the baseline distribution of health parameters in the study population may not reflect those of the general population. However, it is essential to know to which extent the study findings can be generalized to the underlying population from which the subjects had been drawn. In the context of this investigation, the comparison of the distribution of health parameters assessed at baseline with their distribution in the underlying general population, was expected to answer the question whether and to which degree the recruited subjects differed from the general population to which the intervention strategy may be applied in future public health efforts. Therefore, an attempt was made to draw comparisons between the ELF population and published data for relevant reference populations.

For this purpose the following published data were used to provide the relevant benchmark values:

Comparison with German population data from the MONICA investigation

The World Health Organization's MONICA (Multinational **MONI**toring of trends and determinants in **CA**rdiovascular disease) Project had been established in the early 1980s across 21 countries, with 32 MONICA Collaborating Centers (MCC), four of which had been set up in Germany [233]). The purpose of the MONICA project was to identify trends in cardiovascular disease mortality. Each MCC had been tasked to carry out two or three surveys, 5 years apart, of independent random samples drawn from the population of each center's geographic area. Of the 4 German MCCs (Bremen, East Germany, Augsburg and Heidelberg), the data of the latest survey performed in the urban Augsburg population was selected for comparison with the predominantly urban ELF study population. While the Rhein/Neckar population of the Heidelberg MCC was of closer geographic proximity to the ELF study population, the Heidelberg MCC had only carried out the initial survey between September 1983 and July 1987 whereas for the Augsburg urban population the latest data available are from the third survey conducted between October 1994 and July 1995. The age range of the surveyed population included those between 25 and 64 years of age, with no overlap in the subjects sampled for each survey. All MONICA data, selected for the relevant age strata of 45-54 years, are presented together with the ELF equivalents in Table 5a. The MONICA data had been gathered through physical examinations and laboratory analysis using one single dedicated laboratory. The MONICA data have been published in the form of an internet handbook (available at http://www.ktl.fi/publications/monica/surveydb/title.htm).

Table 5a:

Baseline Comparison Of The ELF Sample With The MONICA Study Population

		ELF		MONICA AUU[a]		Δ (*p*)
		value (SD)	N	value (SD)	N	
Height cm	Male	178.2 (6.4)	84	174.7 (5.5)	212	3.5 *p*<0.001
	Female	165.3 (5.1)	33	162.2 (6.2)	217	3.1 *p*<0.01
Weight Kg	Male	91.3 (13.4)	84	83.5 (11.7)	212	7.8 *p*<0.001
	Female	80.2 (15.7)	33	70.8 (13.9)	217	9.4 *p*<0.001
BMI Kg/m^2	Male	28.7 (3.6)	84	27.3 (3.5)	212	1.4 *p*<0.01
	Female	29.3 (5.3)	33	26.9 (5.3)	217	2.4 *p*<0.05
HDL mg/dL	Male	50.7 (10.9)	84	47.5 (14.7)	210	3.2 *p*=0.07
	Female	65.1 (15.4)	31	61.5 (17)	210	3.6 *p*=0.26
TCh mg/dL	Male	224.1 (51.9)	84	241.3 (47.5)	210	-17.2 *p*<0.01
	Female	221.2 (46.1)	31	235.1 (42.5)	210	-13.9 *p*=0.09
TCh/HDL ratio	Male	23.54 (6.42)	84	20.27 (6.99)	210	3.27 *p*<0.001
	Female	30.14 (7.35)	31	26.98 (8.47)	210	3.16 *p*=0.05
BPsys (mmHg)	Male	141.4 (15.2)	81	137.8 (19.0)	212	3.6 *p*=0.12
	Female	139.5 (16.4)	29	133.0 (20.1)	219	6.5 *p*=0.09
BPdia (mmHg)	Male	84.1 (8.9)	81	86.2 (11.9)	212	2.1 *p*=0.14
	Female	79.2 (10.4)	29	82.2 (11.1)	219	3.0 *p*=0.16

Note:
Data are means ± SD unless otherwise noted.
TCH: total cholesterol; HDL: high-density lipoprotein; BMI: body mass index (kg/m^2) BPsys: systolic blood pressure (mmHg); BPdia: diastolic blood pressure (mmHg);
a: Data are taken from the MONICA Study (Multinational **MONI**toring of trends and determinants in **CA**rdiovascular disease MONICA) for the Augsburg urban population third survey conducted between October 1994 and July 1995 and for the age strata 45-54 years [233].

The comparison of baseline values with the MONICA study population suggests that ELF subjects are significantly taller than the MONICA population. While body height is of little relevance to the study objective, it was nevertheless investigated whether this difference might simply reflect a chance finding, or an underlying factor, which may or may not be relevant to the comparison of the two populations. The data of the MONICA population had been sampled from October 1994 to July 1995 and are therefore approximately 15 years older than the data of the ELF study population. Hence, for height, the 15-years younger MONICA cohort provides a more appropriate comparison group, as its years of birth coincide more closely with those of the ELF subjects. The mean height in the 35-44 MONICA age cohort was 176.9 cm and 162.8 cm for men and women respectively. For the men the difference of 1.3 cm between the MONICA and ELF samples was non-significant, with $t(280)=1.50$ and $p=0.13$. For the women the 2.5 cm difference between samples remained significant with $t(256)=2.2$ and $p=0.03$. These data suggest that there exists a significant difference in height between the two female study populations only, a comparison with the data published from the latest 2005 German Microcensus, however, does not support this

conclusion [293]. For the 45-50 age cohorts, the Microcensus reports mean height for men and women of 178 cm and 166 cm respectively, which are almost identical to the mean values of the ELF sample. While tests of significance cannot be performed, as no values for SD have been published for the Microcensus, the difference in height between the two female study populations was attributed to a chance finding with no relevance for this study' objectives and hypotheses.

That the ELF subjects have a significantly elevated BMI is supported not only by comparison with the MONICA study population but also by comparison with the Microcensus publication, which reports population mean BMI values of 26.6 and 24.8 for the male and female 45-50 age cohorts respectively. Despite this elevated body weight status, cholesterol values of the ELF population appear marginally better than those reported for the MONICA population. With a higher level of HDL cholesterol (50.7 vs. 47.5), a significantly lower level of total cholesterol and a significantly lower TCH/HDL ratio, ELF males presented a slightly but significantly more favorable lipid profile. Probably due to the small sample size, this finding could not be replicated in the female ELF participants, who showed the same trends but reaching significance only for TCH and TCH/HDL ratio.

Blood pressure values were not significantly different between the ELF and the MONICA samples, neither for systolic nor for diastolic values.

Comparison with the Finnish Kuopio Ischaemic Heart Disease Risk Factor Study (KIHDS)

Owing to a lack of published population data on VO2peak values for German population groups, available data from the ongoing Kuopio Ischaemic Heart Disease Risk Factor Study (KIHDS) were used for comparison purposes [236]. The data are presented in Table 5b. In analogy to the MONICA study, the KIHDS investigates risk factors, including parameters of physical fitness, and their correlation with atherosclerotic vascular disease. Contrary to the MONICA design, the KIHDS is a longitudinal investigation of a representative random sample of Finnish men aged between 42 and 60 years at study entry between 1984 and 1989. This study provides VO2peak data for 2351 individuals who were grouped according to their CVD health status at baseline into a healthy and an unhealthy group of 1294 and 1057 individuals respectively.

Table 5b:

Baseline Comparison Of The ELF Sample With The Finnish KIHDS Study Population

	ELF	KIHDS[a] healthy men		KIHDS[a] unhealthy men	
	(n=84)[b]	(n=1294)	Δ (*p*)	(n=1057)	Δ (*p*)
Age	50.8 (8.0)	51.8 (5.4)	-1 *p*=0.11	54.2 (4.2)	-3.4 *p*<0.001
BMI	28.7 (3.6)	26.6 (3.4)	2.1 *p*<0.001	27.1 (3.6)	1.6 *p*<0.001
VO2peak ml/kg/min	34.6 (7.2)	32.5 (7.5)	2.1 *p*<0.05	27.3 (7.6)	7.3 *p*<0.001
HDL mg/dL	50.7 (10.9)	50.6 (11.6)	0.1 *p*=0.9	49.1 (11.9)	1.6 *p*=0.23
TCh mg/dL	224.1 (51.9)	226.6 (39.4)	-2.5 *p*=0.5	230.5 (43.3)	-6.4 *p*=0.19
LDL mg/dL	140.8 (46)	155 (37.5)	-14.2 *p*<0.001	158.2 (41)	-17.4 *p*<0.001
TG mg/dL	162.5 (107.3)	108.9 (67.3)	53.6 *p*<0.001	120.4 (77.9)	42.1 *p*<0.001
BPsys[b]	141.4 (15.27)	133.8 (16.1)	7.6 *p*<0.001	134.4 (17.8)	7.0 *p*<0.001
BPdia[b]	84.1 (8.96)	88.8 (10.4)	-4.7 *p*<0.001	88.9 (10.6)	-4.7 *p*<0.001

Note:
TCH: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: Triglycerides; BMI: body mass index (kg/m^2); VO2peak: peak oxygen consumption; BPsys: systolic blood pressure (mmHg); BPdia: diastolic blood pressure (mmHg);

a: data from the ongoing Kuopio Ischaemic Heart Disease Risk Factor Study (KIHDS) [236].
b: Blood pressure values were available for 81 participants of the ELF population;

These data show that the male ELF participants were similarly aged as the healthy Finnish men but approximately 3.5 years younger than the unhealthy Finnish cohort. The ELF men were significantly more overweight with a BMI of 28.7 vs. 26.6 and 27.1 in the Finnish healthy and unhealthy cohorts respectively. Compared with the healthy Finnish cohort VO2peak of the ELF men was only marginally (2.1 ml/kg/min) but significantly higher. The difference to the unhealthy Finnish men however was in excess of 2 METs (7.3 ml/kg/min).

Contrary to the comparison with the MONICA population, the TCH and HDL values of the ELF men were almost identical to those observed in both Finnish groups, with a significantly lower concentration of LDL cholesterol in the ELF men, and a substantially higher concentration of TG, the latter possibly reflecting the overweight status of the ELF subjects.

Systolic blood pressure was significantly higher in the ELF men whereas diastolic blood pressure was significantly lower. Both differences were of a magnitude of clinical relevance.

HYPOTHESES TESTING

Testing for effects between baseline and follow-up shifts the focus from avoiding type II to avoiding type I errors. Consequently, all within-group tests for significance of change from baseline to follow-up, and for between-group tests of significance of the difference of changes were repeated on transformed data when the raw data were found to violate the normality assumption.

Hypothesis 1: Adherence

As presented in Table 4a, 89 participants (76%, CI: 68.3% to 83.7%) satisfied all three criteria required for being classified as having an operational controlled feedback loop (CFL+) at follow-up:

- *latency:* last-login not more than 7 days prior to date of follow-up assessment
- *duration:* having maintained an active log with weekly logins for 3 or more consecutive months (90 days)
- *volume:* having recorded 60 minutes or more of weekly high-intensity exercise performed in bouts of each 20 minutes or more

To determine the effect of the latency condition on the parameter of adherence, a comparison was made between the proportion of individuals who met the CFL+ conditions and the proportion who achieved at least 80% of the prescribed cumulative 25-weeks PA volume of 1,500 minutes (25 weeks x 60'/week), and irrespective of meeting the latency condition. Expressing adherence as a percentage of prescribed exercise volume, and/or dichotomizing adherence along an arbitrary %-of-volume cutoff is frequently used in published studies on exercise interventions [294-296]. The results of the comparison are presented in Table 6a. While the conventional adherence definition yields a higher but not significantly different proportion of adherent subjects (82% vs, 76%), it incorrectly identifies the CFL status of 17 individuals. Of these, 12 subjects who did not meet the latency requirement at the end of the intervention would have been identified as adherent, and 5 CFL+ subjects would have been identified as non-adherent.

Table 6a:

Comparison Of Adherence By Definitions Of CFL-Status vs. Exercise Volume

Adherence Definition			
CFL+	80% of Volume[a]	*p* value for difference	Misclassified
N=89	N=96		N=17
0.76 (CI 0.68 – 0.84)	0.82 (CI 0.75 – 0.89)	$p(z=-1.12) = 0.26$	0.14 (CI 0.08 – 0.21)

a: Proportion of adherent individuals if cut-off for adherence is defined as 80% of prescribed exercise volume

The proportion of CFL+ subjects is significantly better than the 55% (CI 0.39-0.72) adherence rate achieved in a comparable worksite intervention, in which 36 out of 73 enrolled individuals had been randomized to a 24-weeks PA intervention consisting of 3 weekly 20-minutes high intensity aerobic workouts in addition to strength training [235]. The difference in adherence was significant, two-tailed, at $p(z=2.37)<0.05$.

Maintaining the latency condition, while simultaneously increasing the volume and duration conditions, helps to determine (a) the proportion of individuals who have accumulated a larger intervention dose, and (b) whether this dose correlates with an increased health benefit. Stratification of participants into CFL+ and CFL- groups based on continuous login records of 4 and 5 months (120 and 150 days respectively), with latency and volume conditions as defined for the 3-months strata, yielded proportions of CFL+ groups of 73.5% and 56.4% respectively (see Table 3).

In this context it was desirable to investigate the actual amount of time spent on exercise vs. the specified minimum requirement of 3x20 minutes weekly on interval training. Table 6b presents the data as medians and IQR due to the substantial deviation from the normal distribution as evidenced in Figure 5.

Table 6b

Self-reported Time Spent (Minutes Per Week) In Aerobic Exercise

	Median	IQR[a]	Smallest - Largest
CFL90 N=89	158.8	112.0 to 241.8	60.0 – 528.5
CFL120 N=86	158.8	112.0 to 241.8	60.0 – 464.1
CFL150 N=66	163.1	113.6 to 250.2	67.0 – 464.1

Note
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
a: IQR = Inter-Quartile Range

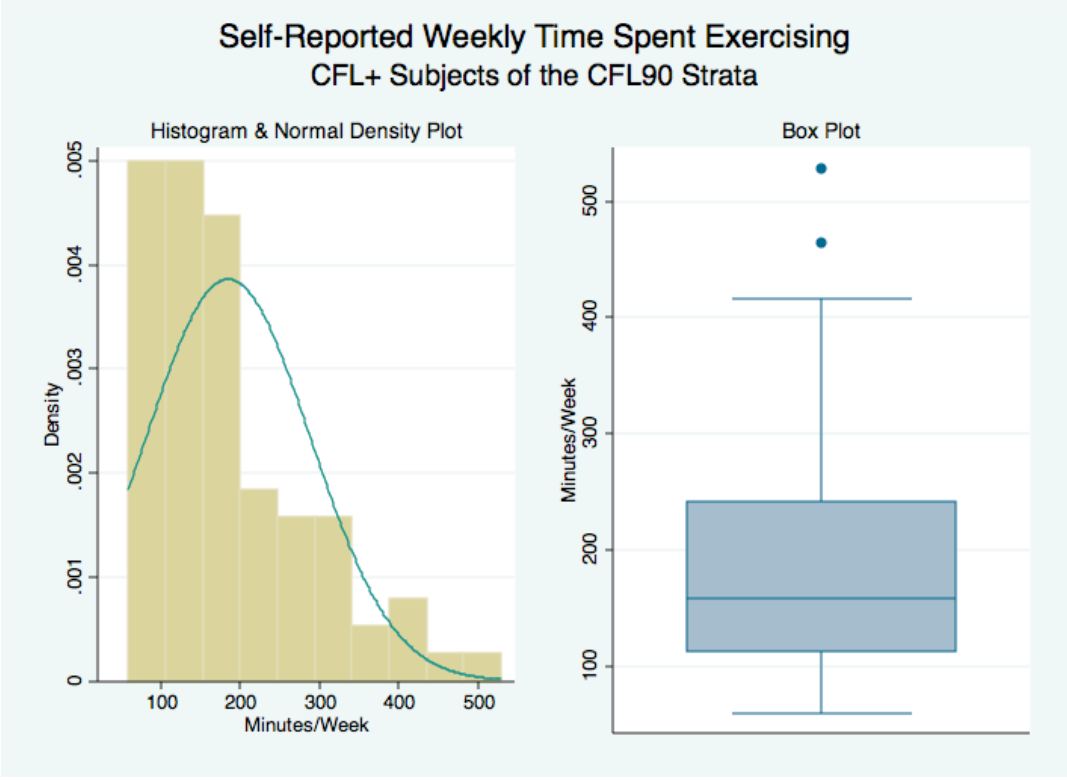

Figure 5. **Self-reported weekly time spent on exercise by the 89 adherent subjects**

These data demonstrate that the majority of CFL+ participants spent a substantially larger amount of time exercising than what had been prescribed as the minimum of 60' per week. Since the self-reporting technique did not enable participants to differentiate between levels of exercise intensity, the calorific equivalent of the reported exercise volume cannot be determined.

Hypothesis 2: Peak Oxygen Uptake

VO_2peak values were normally distributed within both CFL groups of each strata.

Paired samples t-tests were conducted to evaluate whether the participants had increased VO_2peak significantly from baseline to follow-up. Data of those participants for whom one or both tests had to be terminated prematurely, were not considered for analysis.

The results indicate that the CFL+ participants of all strata increased their cardiopulmonary fitness significantly by close to 1 MET, whereas no significant change was observable among the CFL- participants. The test results are displayed in Table 7.

Independent samples t-tests were conducted to evaluate the hypothesis that the mean improvement in VO2peak from baseline to follow-up was significantly higher in the CFL+ group compared to the CFL- group of each strata. The results indicate that the increase in cardiopulmonary fitness observed among the CFL+ participants was significantly different from the change of this parameter observed in the corresponding CFL- groups of each strata. The results are shown in Table 7.

Table 7

Change In VO2peak

	CFL- (non-adherent)			CFL+ (adherent)			
	pre	post	change	pre	post	change	diff of change* (SE)
CFL90 (N: 23/73)[a]	32.51 ±7.96	32.09 ±7.92	-0.42 NS	32.8 ±8.1	36.1 ±9.2	3.3 t(72) = 7.13, *p*<0.001	3.7 (0.66) t(70.27)=-5.67, *p*<0.001
CFL120 (N: 26/70)[b]	32.43 ±7.88	32.62 ±7.91	0.19 NS	32.8 ±8.1	36.1 ±9.3	3.2 t(69)=6.73, *p*<0.001	3.0 (0.73) t(68.6)=-4.22, *p*<0.001
CFL150 (N: 42/54)[c]	32.4 ±8.5	33.5 ±9.9	1.1 NS	32.9 ±7.6	36.4 ±8.2	3.5 t(53)=6.82, *p*<0.001	2.4 (0.79) t(88.2)=-3.01, *p*<0.01

Note: Data are means ± SD unless otherwise noted.
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
* Unequal variances were assumed and Welch's approximation for estimating degrees of freedom was applied
a: 23 non-adherent subjects vs. 73 adherent subjects; **b:** 26 non-adherent subjects vs. 70 adherent subjects;
c: 42 non-adherent subjects vs. 54 adherent subjects;

Improvement in CRF: A True Intervention Effect Or An Arithmetic Artifact?

VO_2peak is conventionally expressed in milliliters of oxygen consumption per minute and per kilogram of bodyweight. Hence, any post-weight loss increase in VO_2peak could be merely an arithmetic artifact without any concomitant real increase of CRF. Since it is a body's lean mass, not its fat content, which delivers the muscular work and power output, the correlation of VO_2 consumption with lean body mass provides a more adequate value to assess the true change in cardiopulmonary fitness. As these values are hardly reported in published literature, a comparison with reference populations is currently impossible. However, it is still useful to investigate in this study population, whether the measured increase in VO_2peak represented a true increase in cardiopulmonary fitness or merely an arithmetic artifact of weight loss. If the latter was true, there would be no increase in the LBM-based VO_2peak value. For this purpose the aforementioned calculations were repeated using the modified VO_2peak value for lean body mass, the latter having been determined by psBIA analysis. In the CFL90 strata, CFL+ subjects showed an increase of VO2peak of 5.3 ml/kg/min whereas the CFL- participants showed a non-significant decrease of 1.8 ml/kg/min.

The results for all strata are presented in Table 8, which shows that across all three CFL strata, there were no significant changes observed in the CFL- groups, whereas the CFL+ participants had significantly increased their VO_2peak values. The differences of change between groups remained significant for all strata.

Table 8

Change Of VO2peak Per Kg Lean Body Mass

	CFL- (non-adherent)			CFL+ (adherent)			
	pre	post	change	pre	post	change	diff of change* (SE)
CFL90 (N: 23/73)[a]	85.12 ±14.08	83.25 ±14.08	-1.8 NS	86.78 ±16.12	92.10 ±16.53	5.31 t(72)=5.11, *p*<0.001	7.18 (0.90) t(94)=-3.59, *p*<0.001
CFL120 (N: 26/70)[b]	84.82 ±15.01	84.43 ±15.25	-0.39 NS	86.96 ±15.88	92.04 ±16.38	5.07 t(69)=4.72, *p*<0.001	5.46 (1.78) t(55.1)=-3.06, *p*<0.01
CFL150 (N: 42/54)[c]	85.16 ±16.13	85.84 ±17.36	0.68 NS	87.34 ±15.27	93.19 ±14.9	5.85 t(53)=4.64, *p*<0.001	5.17 (1.75) t(93.8)=-3.03, *p*<0.01

Note:
Data are means ± SD unless otherwise noted.
* Unequal variances were assumed and Welch's approximation for estimating degrees of freedom was applied
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
a: 23 non-adherent subjects vs. 73 adherent subjects; **b:** 26 non-adherent subjects vs. 70 adherent subjects;
c: 42 non-adherent subjects vs. 54 adherent subjects;

The boxplot of the VO2peak values (Figure 6), based on body weight and on LBM, indicated that two outliers (VO2peak per body weight) may have influenced the results. These outliers represented two highly motivated individuals whose self-imposed training intensity and volume exceeded the prescription substantially. To test whether the changes in VO_2peak

observed intra-group (baseline to follow-up for the CFL+ groups) and inter-group (CFL+ vs. CFL- for each strata) remained significant after removal of these outliers, all analyses were repeated not considering the data of these two individuals.

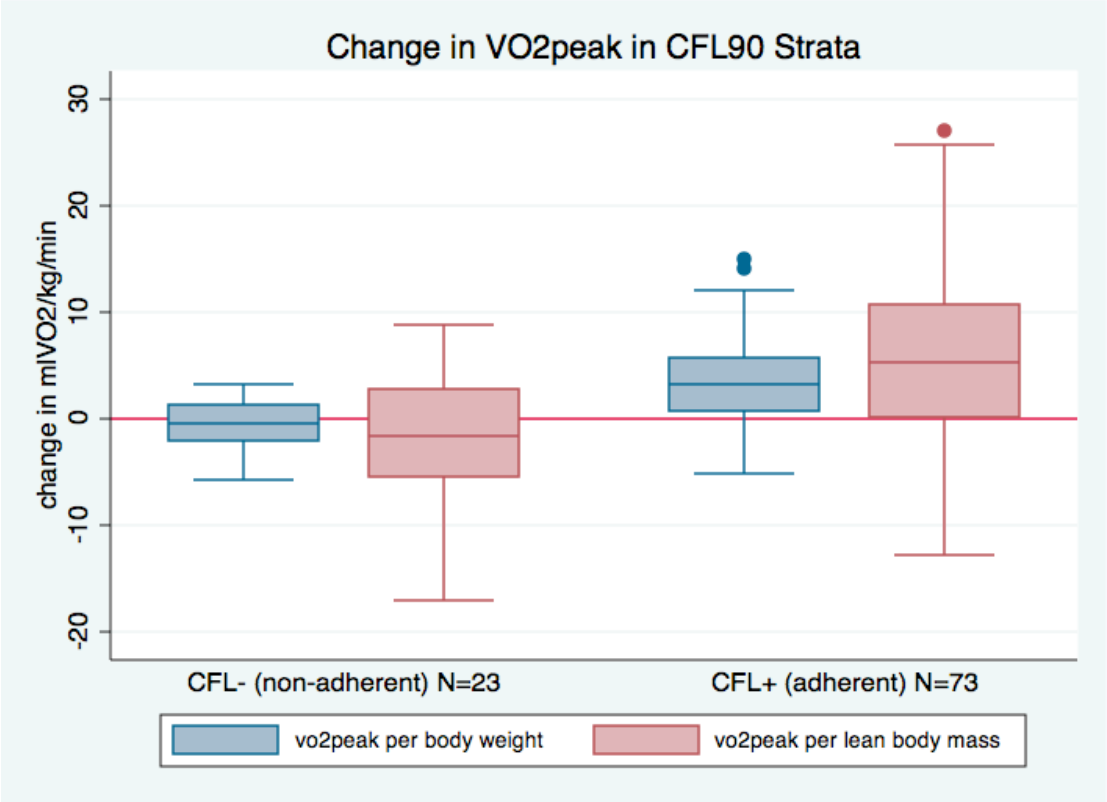

Figure 6: **Change Of Maximal Oxygen Consumption In The CFL90 Strata**

After removal of the outliers, changes in VO2peak from baseline to follow-up, though marginally attenuated, remained significant in the CFL+ groups of each strata and non-significant in the CFL- groups. Between-group differences in change of VO2peak, though marginally attenuated, remained significant for all 3 strata. As one of the two individuals had not met the duration criterion for inclusion in the CFL+ group of the CFL150 strata, the values of this individual were removed from the CFL- group of this strata.

Table 9 displays the results of these analyses, and Figure 7 illustrates the effect of removing the outliers from the sample.

Table 9

Change Of VO2peak after removal of outliers

	CFL- (non-adherent)			CFL+ (adherent)			
	pre	post	change	pre	post	change	diff of change* (SE)
CFL90 (N: 23/71)[a]	32.51 ±7.96	32.09 ±7.92	-0.42 NS	32.68 ±8.1	35.71 ±9.02	3.03 t(70) = 7.12, *p*<0.001	3.45 (0.63) t(59.98)=-5.44, *p*<0.001
CFL120 (N: 26/68)[b]	32.43 ±7.88	32.62 ±7.91	0.19 NS	32.72 ±8.19	35.67 ±9.11	2.94 t(67)=6.68, *p*<0.001	2.74 (0.69) t(59.1)=-3.93, *p*<0.001
CFL150 (N: 41/53)[c]	32.2 ±8.52	32.96 ±9.43	0.76 NS	32.98 ±7.76	36.27 ±8.19	3.28 t(52)=6.86, *p*<0.001	2.5 (0.70) t(88.3)=-3.59, *p*<0.001

Data are means ± SD unless otherwise noted.
* Unequal variances were assumed and Welch's approximation for estimating degrees of freedom was applied
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
a: 23 non-adherent subjects vs. 71 adherent subjects; **b:** 26 non-adherent subjects vs. 68 adherent subjects;
c: 41 non-adherent subjects vs. 53 adherent subjects;

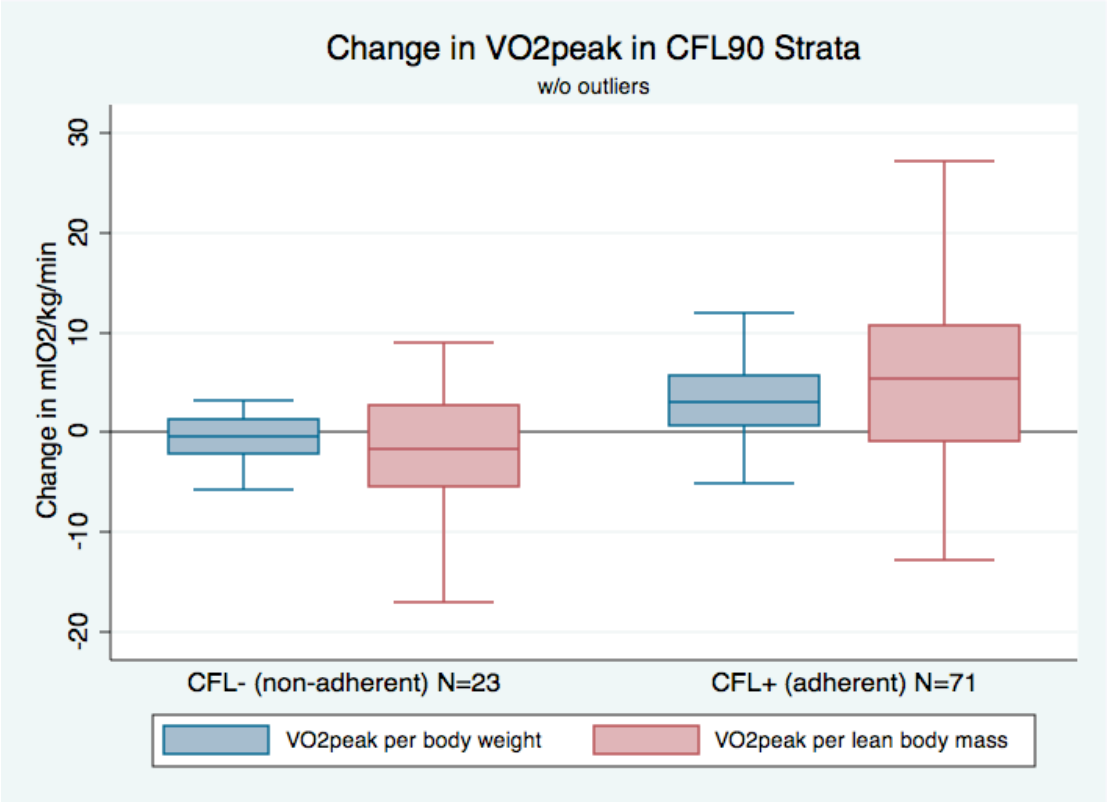

Figure 7: **Change Of Maximal Oxygen Consumption In The CFL90 Strata w/o Outliers**

Addressing the Issue of Gender Specific Differences in CRF

The evaluation of cardiopulmonary fitness in mixed-gender groups may be affected by gender specific differences in muscle fiber composition and muscle mass. These differences are typically reflected in lower mean values of VO_2peak in women, when VO_2peak is expressed in minute oxygen consumption per kg body weight. Compared to men, women have a larger

proportion of fat mass and consequently a smaller proportion of muscle mass, which partly explains the lower VO_2peak values in females.

Figure 8 displays the boxplots for VO_2peak based on body weight as well as on LBM at baseline by gender. Visual inspection suggests that the gender difference in VO_2peak is attenuated when the latter is calculated based on LBM rather than on body weight. While the between-gender difference remains significant (see Table 10), Cohen's d, as a measure of effect size, is dramatically lower in the LBM-based VO_2peak calculation. This observation suggests that, when evaluating intervention effects on cardiopulmonary fitness as the dependent variable in mixed-gender samples with insufficiently sized gender-specific sub-groups, using lean body mass as the reference base for the calculation of VO_2peak may be preferable to the conventionally used base of total body weight.

Table 10

Peak Oxygen Consumption In Relation To Body Weight And Lean Body Mass

	male (N=72)	female (N=29)	difference	Cohen's d
VO2peak by body weight	35.41 ±6.85	25.35 ±5.40	10.05 t(99)=7.05, p<0.001	1.56
VO2peak by lean body mass	88.45 ±15.53	81.14 ±13.76	7.30 t(99)=2.20, p<0.05	0.49

Note: Values for all participants with valid peak oxygen consumption data from tests at baseline to volitional exhaustion

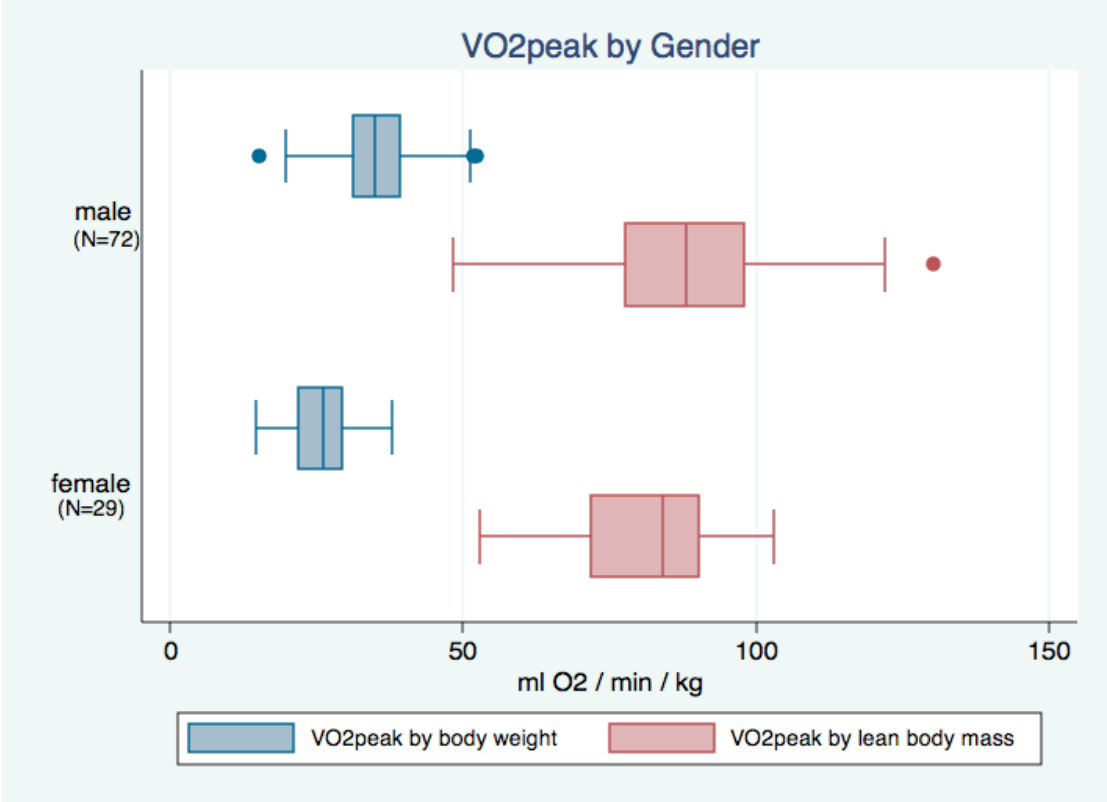

Figure 8. **Gender comparison of peak Oxygen consumption by body weight and lean body mass**

Intervention Effect on VO_2peak expressed as Percent of Normal Values

To eliminate the gender specific differences from the evaluation of intervention effects on VO_2peak, the latter was expressed as a percentage of gender- and age-specific normal values. The formula, published and validated by Cooper et al. [297], were used for this analysis.

Equation 7:
$$VO_2\max(men) = 50.02 - (0.394 \times age) ml/kg/\min$$
$$VO_2\max(women) = 42.83 - (0.371 \times age) ml/kg/\min$$

Independent-samples t-tests were conducted to evaluate whether CFL+ and CFL- groups differed significantly at baseline when expressing cardiopulmonary fitness as a percentage of the age and gender based normal values. Again, the data of those participants for whom one or both tests had to be terminated prematurely, were not considered for analysis.

Shapiro-Wilk tests confirmed normality of the distributions of VO_2peak as a percentage of normal values for all CFL groups in each strata and at baseline and follow-up.

The results of the independent samples t-tests are presented in Table 11.

Table 11.

Baseline Comparison Of VO_2peak Expressed As Percent Of Age And Gender Specific Normal Values.

	CFL- (non-adherent) VO_2peak as % of normal value (SD)	CFL+ (adherent) VO_2peak as % of normal value (SD)	difference	*p*-value, two-tailed
CFL90 strata[a]	109.29 (19.52)	115.09 (21.88)	5.8	0.25
CFL120 strata[b]	109.77 (20.96)	115.15 (21.5)	5.38	0.27
CFL150 strata[c]	112.06 (21.38)	114.97 (21.49)	2.91	0.51

CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
a: 23 non-adherent subjects vs. 73 adherent subjects; **b:** 26 non-adherent subjects vs. 70 adherent subjects;
c: 42 non-adherent subjects vs. 54 adherent subjects;

While the CFL+ groups tended to be slightly fitter, the differences between mean values of VO_2peak, the latter being expressed as % of normal values, were not significant.

Subsequently, paired samples t-tests were conducted to evaluate whether the participants had increased VO2peak, expressed as percent of normal values, significantly from baseline to follow-up. Independent samples t-tests were conducted to investigate the significance of inter-group differences of these changes from baseline to follow-up. The results of the analyses are presented in Table 12 and Figure 9.

Table 12

Change in VO_2peak (expressed as percent of normal value) from baseline to follow-up

	CFL- (non-adherent)		CFL+ (adherent)		
	Mean (SD)	95% CI	Mean (SD)	95% CI	*p*-value
CFL90	-1.33 (7.74)	-4.68 to 2.0	11.60 (13.89)	8.36 to 14.84	<0.001
CFL120	0.83 (9.55)	-3.02 to 4.69	11.35 (14.12)	7.98 to 14.71	<0.001
CFL150	3.42 (13.28)	-0.72 to 7.58	12.44 (12.98)	8.9 to 15.99	<0.001

CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
a: 23 non-adherent subjects vs. 73 adherent subjects; **b:** 26 non-adherent subjects vs. 70 adherent subjects;
c: 42 non-adherent subjects vs. 54 adherent subjects

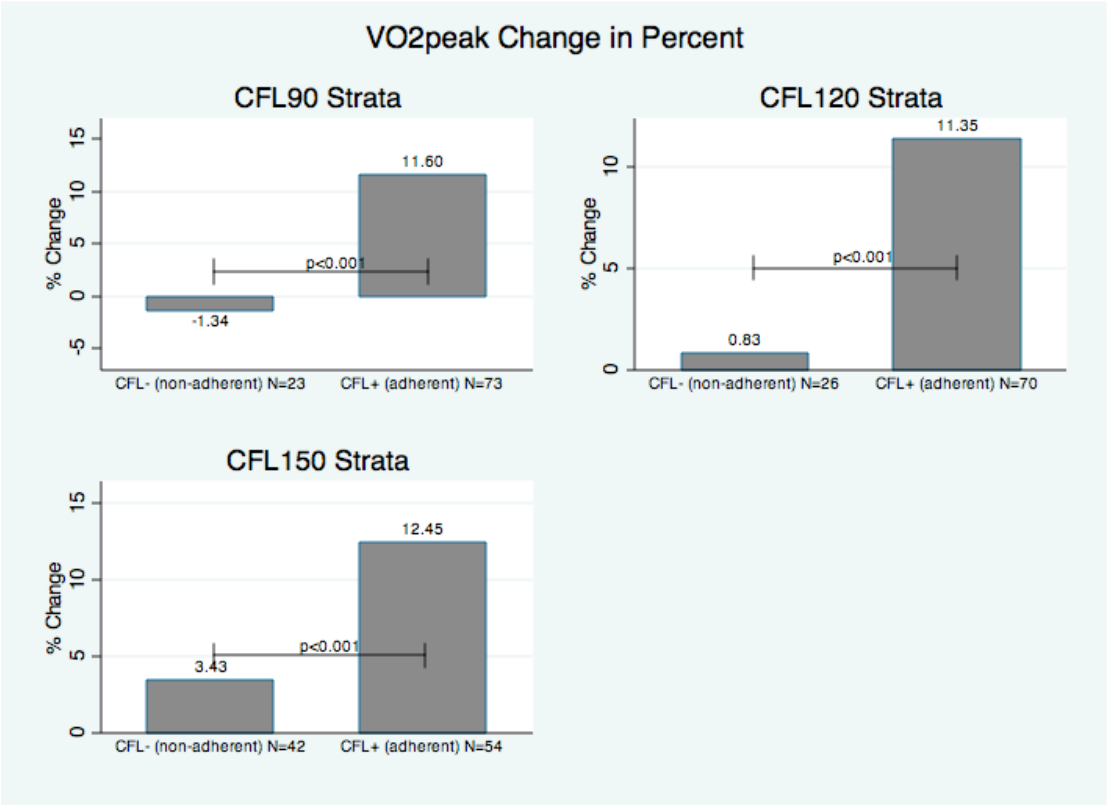

***Figure 9*. Relative Change of VO2peak From Baseline To Follow-Up For All Strata**

With no significant differences between CFL groups at baseline, the group of actively self-monitoring participants witnessed a mean increase in VO_2peak (expressed as a percentage of age and gender predicted normal values) of close to 12 %, whereas no significant change of VO2peak increase was observed in the CFL-groups of the CFL90 and CFL 120 strata. The CFL- group of the CFL150 strata witnessed a 4.3% increase which was borderline significant at p=0.046. This reflects the inclusion of participants into this strata's CFL- group, who are considered actively self-monitoring in the CFL90 strata but who had not met the duration criterion of the CFL150 strata for inclusion into the strata's CFL+ group. These individuals'

improvements of cardiorespiratory fitness increased the group mean of the CFL- group in this strata.

A two-way contingency table analysis was conducted to evaluate the odds ratio of improving cardiorespiratory fitness to a clinically relevant degree between the two CFL± groups within each strata. The two variables were improvement of CRF (dichotomized to < or ≥ 3.5 ml O_2/min/kg of body weight) and CFL status (CFL+ or CFL-). Table 13 presents the results. While 32 of the 73 CFL+ participants had increased the CRF by at least 3.5 ml O_2/min/kg, none of the CFL- participants had achieved such increase. As none of the expected cell frequencies was less than 5, results of the chi-squared test were accepted for the evaluation of significance of differences. CFL status and CRF improvement in excess of 3.5ml O_2/min/kg were found to be significantly related, Pearson χ^2 (1, N=96)=15.12, p<0.001. As none of the CFL- participants had achieved the CRF increase, the odds ratio was not calculated.

Table 13.

Odds Ratio For Change Of VO2peak by ≥ 1 MET or < 1MET And By CFL Group

	CFL- (non-adherent)	CFL+ (adherent)	*p* value	OR	95% CI
CFL90 (N: 23/73)	0 (0 of 23)	43.8% (32 of 73)			
CFL120 (N: 26/70	11.5% (3 of 26)	41.4% (29 of 70)	*p*<0.01	5.42	1.48 to 19.77
CFL150 (N: 42/54)	19.0% (8 of 42)	44.4% (24 of 54)	*p*<0.01	3.4	1.32 to 8.69

Note:
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
a: 23 non-adherent subjects vs. 73 adherent subjects; **b:** 26 non-adherent subjects vs. 70 adherent subjects;
c: 42 non-adherent subjects vs. 54 adherent subjects;

Hypothesis 3: Body Weight Status

Inspection of the anthropometric and body composition parameters for normality, using Shapiro-Wilk tests, histograms and Q-Q plots, confirmed normal distributions for BMI and body weight, and minor deviations from normality for body fat at follow-up.

Figure 10 shows the box plots of BMI values (at baseline and at follow-up) for participants with baseline BMI ≥ 25 for the CFL90 strata. Visual inspection suggests a reduction in BMI in the CFL+ group compared to no reduction in the CFL- group.

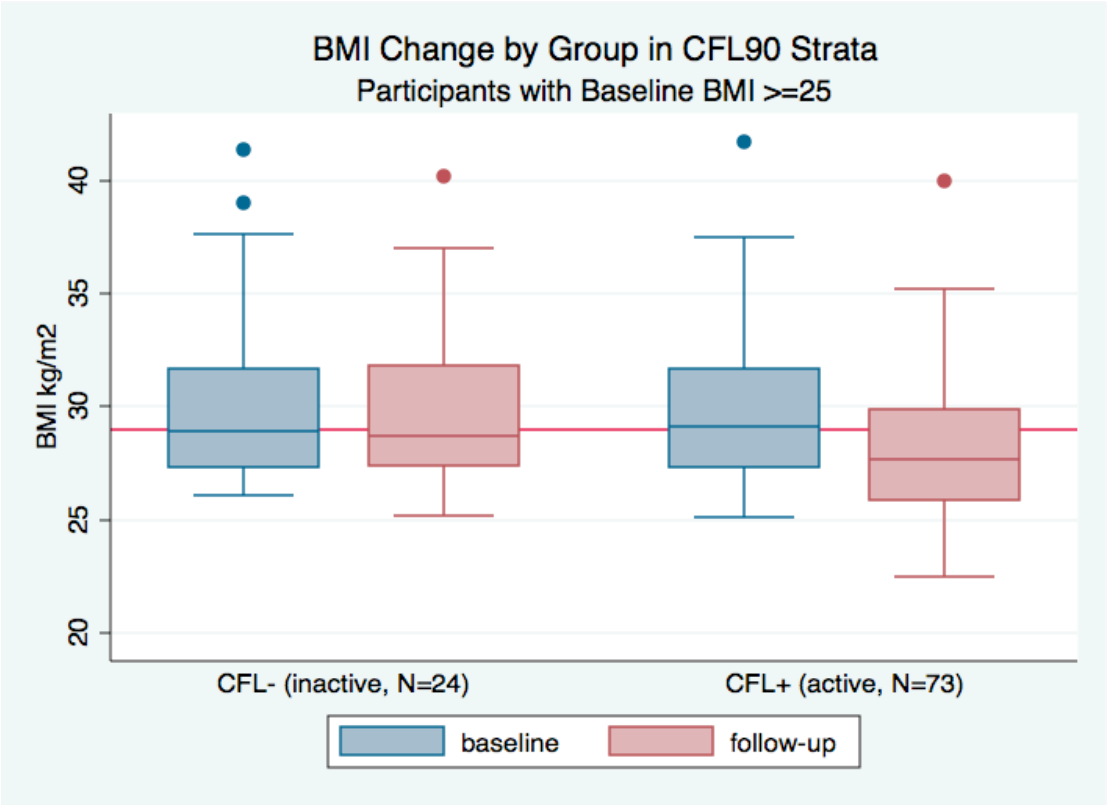

Figure 10. **BMI At Baseline And Follow-Up By CFL Group**

Figure 11 displays the box plots for BMI change in the CFL90 strata. As was the case for VO_2peak, outliers affected the distribution, which deviated from normal in the CFL+ groups.

Removal of the three outliers for BMI change normalized the distribution of weight change, BMI change and fat change in all groups of all strata. The outliers represent two individuals who had reduced their BMI by 4.8 points and one individual who had reduced his BMI by 9.8 points. Two of these three outliers represent the same two individuals mentioned in the discussion of VO2peak analysis.

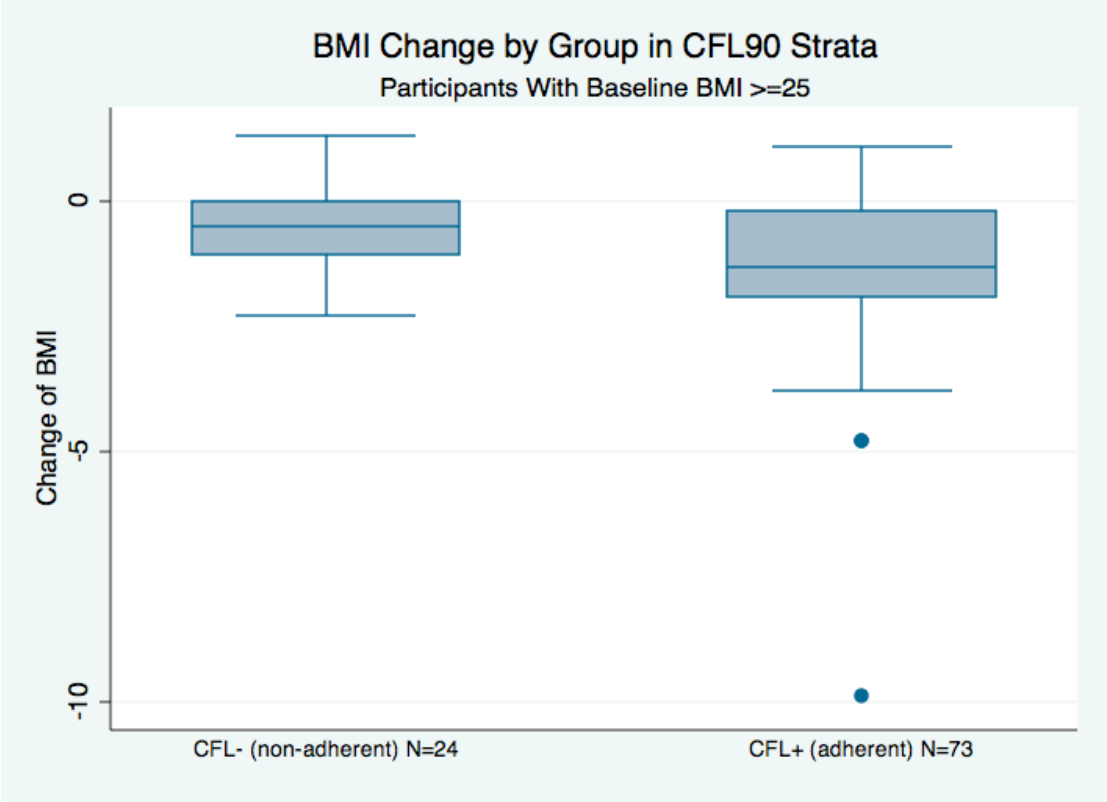

***Figure 11*. BMI Change By CFL Group**

Paired samples t-tests were conducted for both CFL groups of each CFL strata to evaluate whether the participants had decreased body weight, body fat and BMI from baseline to follow-up. Table 14 demonstrates that the changes in body weight, BMI and body fat were significant for all CFL groups within each strata, with the CFL+ groups witnessing a substantially larger decrease for all three variables.

Independent-sample t-tests, conducted under the assumption of equal variances (Levene's tests for equality of variances were non-significant for all three variables of change), confirmed the hypothesis that the between-group differences were significant. The results for changes in body weight, BMI and body fat are presented Table 14.

To test whether the between-group changes in body weight and fat and BMI remained significant after removal of the three outliers, all analyses were repeated for the CFL90 strata not considering the data of these three individuals. The results are presented in Table 15. After removal of the outliers, between-group changes in BMI, body fat and weight, though marginally attenuated, remained significant favoring the hypothesis of significant differences between CFL groups.

Table 14:

Parameters Of Body Weight Status (for subjects with baseline BMI ≥ 25)

	CFL- (inactive)			CFL+ (active)			
Body Weight (kg)	pre	post	change	pre	post	change	diff of change* (SE)
CFL90 (N: 24/73)[a]	94.1 ±13.6	92.6 ±12.1	-1.5 t(23)=-2.75, *p*<0.05	90.8 ±13.0	86.5 ±12.4	-4.3 t(72)=-7.33, *p*<0.001	2.8 (0.8) t(76.8)=3.4, *p*<0.01
CFL120 (N: 27/70)[b]	94.4 ±13.7	92.5 ±11.8	-1.9 t(26)=-3.11, *p*<0.001	90.5 ±12.9	86.2 ±12.4	-4.3 t(69)=-7.11, *p*<0.001	2.4 (0.8) t(77.5)=2.8, *p*<0.01
CFL150 (N: 43/54)[c]	93.4 ±13.2	91.0 ±12.1	-2.4 t(42)=-4.25, *p*<0.001	90.1 ±13.1	85.5 ±12.4	-4.6 t(53)=-6.48, *p*<0.001	2.2 (0.9) t(95.7)=2.4, *p*<0.05
BMI (kg/m²)							
CFL90 (N: 24/73)[a]	30.3 ±4.3	29.9 ±3.9	-0.4 t(23)=2.53, *p*<0.05	29.7 ±3.4	28.3 ±3.3	-1.4 t(72)=-7.33, *p*<0.001	0.9 (0.2) t(77)=3.59, *p*<0.001
CFL120 (N: 27/70)[b]	30.4 ±4.2	29.8 ±3.8	-0.6 t(26)=-2.9, *p*<0.05	29.7 ±3.3	28.3 ±3.3	-1.4 t(69)=-7.12, *p*<0.001	0.8 (0.2) t(79.3)=3.01, *p*<0.01
CFL150 (N: 43/54)[c]	30.0 ±3.7	29.3 ±3.5	-0.7 t(42)=-4.2, *p*<0.001	29.8 ±3.6	28.3 ±3.4	-1.5 t(53)=-6.45, *p*<0.001	0.8 (0.3) t(94.3)=2.62, *p*<0.05
Body Fat (kg)							
CFL90 (N: 24/73)[a]	28.6 ±10.0	27.4 ±9.1	-1.2 t(23)=-2.75, *p*<0.05	27.3 ±8.1	24.0 ±8.2	-3.3 t(72)=-7.42, *p*<0.001	2.1 (0.6) t(73.2)=3.3, *p*<0.01
CFL120 (N: 27/70)[b]	28.3 ±10.0	26.8 ±9.0	-1.5 t(26)=-3.11, *p*<0.01	27.4 ±8.0	24.1 ±8.3	-3.3 t(69)=-7.19, *p*<0.001	1.7 (0.6) t(73.8)=2.6, *p*<0.01
CFL150 (N: 43/54)[c]	28.2 ±9.3	26.4 ±8.8	-1.8 t(42)=-4.4, *p*<0.001	27.2 ±8.1	23.7 ±8.1	-3.5 t(53)=-6.5, *p*<0.001	1.6 (0.6) t(95.2)=2.4, *p*<0.05

Note:
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
BMI: body mass index (kg/m²)
a: 24 inactive subjects vs. 73 active subjects; **b:** 27 inactive subjects vs. 70 active subjects; **c:** 43 inactive subjects vs. 54 active subjects;

Table 15

Absolute Changes Of Body Weight Status By CFL Group (for subjects with baseline BMI ≥25) With and W/O Outliers.

	CFL- (non-adherent)		CFL+ (adherent)		difference	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SE)	*p*-value (two-tailed)
BMI (kg/m²)						
CFL90 (N: 24/73)[a]	-0.45 (0.88)	-0.83 to -0.08	-1.4 (1.64)	-1.79 to -1.02	0.95 (0.35)	*p*<0.01 t(95)=2.7
CFL90 w/o outliers (24/70)			-1.19 (1.17)	-1.47 to -0.9	0.73 (0.26)	*p*<0.01 t(92)=2.78
CFL120 (N: 27/70)[b]	-0.57 (1.01)	-0.97 to -0.17	-1.4 (1.65)	-1.79 to -1.01	0.83 (0.34)	*p*<0.05 t(95)=2.45
CFL150 (N: 43/54)[c]	-0.74 (1.15)	-1.1 to -0.38	-1.5 (1.72)	-1.98 to -1.04	0.77 (0.30)	*p*<0.05 t(95)=2.51
Body Weight (Kg)						
CFL90 (N: 24/73)[a]	-1.53 (2.73)	-2.69 to -0.38	-4.32 (5.04)	-4.58 to -2.68	2.78 (1.08)	*p*<0.05 t(95)=2.58
CFL90 w/o outliers (N: 24/70)			-3.65 (3.67)	-4.53 to -2.77	2.11 (0.82)	*p*<0.05 t(92)=2.58
CFL120 (N: 27/70)[b]	-1.90 (3.17)	-3.16 to -0.64	-4.30 (5.06)	-5.51 to -3.09	2.4 (1.04)	*p*<0.05 t(95)=2.29
CFL150 (N: 43/54)[c]	-2.41 (3.71)	-3.55 to -1.26	-4.66 (5.22)	-6.03 to -3.18	2.19 (0.94)	*p*<0.05 t(95)=2.32
Body Fat (Kg)						
CFL90 (N: 24/73)[a]	-1.20 (2.15)	-2.11 to -0.29	-3.28 (3.77)	-4.16 to -2.4	2.07 (0.81)	*p*<0.05 t(95)=2.55
CFL90 w/o outliers (N: 24/70)			-2.77 (2.70)	-3.41 to -2.12	1.56 (0.61)	*p*<0.05 t(92)=2.55
CFL120 (N: 27/70)[b]	-1.50 (2.50)	-2.49 to -0.51	-3.25 (3.78)	-4.15 to -2.35	1.75 (0.78)	*p*<0.05 t(95)=2.22
CFL150 (N: 43/54)[c]	-1.84 (2.75)	-2.69 to -1.0	-3.50 (3.95)	-4.58 to -2.42	1.65 (0.70)	*p*<0.05 t(95)=2.32

Note:
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
BMI: body mass index (kg/m²)
a: 24 inactive subjects vs. 73 active subjects; **b:** 27 inactive subjects vs. 70 active subjects; **c:** 43 inactive subjects vs. 54 active subjects;

Contribution of Body Fat to Weight Loss

Body fat is the target tissue of body weight reduction efforts, which ideally maintain lean body mass. It is therefore desirable to investigate whether those participants, who had lost a clinically relevant amount of body weight, had achieved this weight reduction primarily through loss of body fat. The minimum amount of body weight reduction was set at 4 kg or more, based on published evidence that this amount of weight loss generated measurable

reductions of blood pressure [298, 299] and blood lipids [300]. For the 41 participants who met this weight loss criterion, the mean proportion of fat loss of the total weight loss in this sample was 76.3% (SD= 16.09%, 95% CI 71.8% to 82.0%).

This 76.3% contribution of fat loss to overall weight loss is not significantly different from the published 80% observed in a 3-months energy-deficit controlled exercise intervention among 16 obese (mean BMI and body weight of 32.3 and 101.5 kg respectively) men [301]. One-sample t-test was not significant with t(40)=-1.6, p=0.11.

Figure 12 was created to illustrate the relative proportion of fat from total weight loss in a clinically interesting subgroup of the 28 CFL+ participants who had entered the study with a BMI of 30 or greater. Each pair of bars represents the weight and fat change (in kg) of one participant. This chart illustrates, that loss of body fat was the predominant cause of the overall weight loss in almost all weight-reducing individuals.

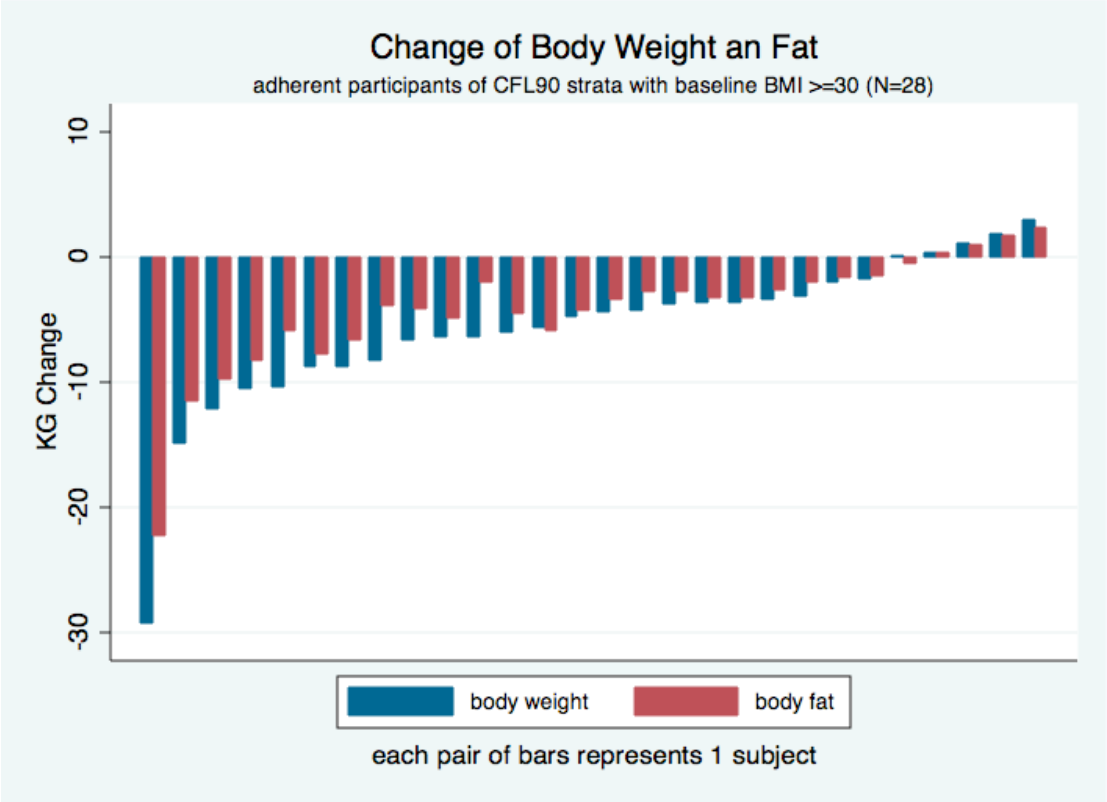

***Figure 12*. Contribution of body fat to weight loss**

A two-way contingency table analysis was conducted to evaluate whether weight loss of a clinically relevant degree was different between the two CFL groups within each strata. The two variables were weight loss (dichotomized to < or ≥ 5% of body weight at baseline) and CFL status (CFL+ or CFL-). As none of the expected cell frequencies was less than 5, results of the chi-squared test were accepted for the evaluation of significance of differences. CFL status and weight loss in excess of 5% body weight were found to be significantly related,

Pearson χ^2 (1, N=115)=9.37, p<0.01. Follow-up logistic regression was conducted to determine the 95% confidence interval of the odds ratio. The results are presented in Table 16.

Table 16.

Odds Ratio For Change Of Body Weight by ≥ 5% or < 5% And By CFL Group

	CFL- (non-adherent)	CFL+ (adherent)	*p* value	OR	95% CI
CFL90	8.3% (2 of 24)	42.4% (31 of 73)	*p*<0.01	8.11	1.77 to 37.12
CFL120	14.8% (4 of 27)	41.4% (29 of 70)	*p*<0.05	4.06	1.27 to 13.01
CFL150	20.9% (9 of 43)	44.4% (24 of 54)	*p*<0.05	3.02	1.21 to 7.5

Note:
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months

Hypothesis 4: Cardiovascular Risk Factors

Lipids

The results for the within- and between-group evaluations of intervention effects on the lipid outcome parameters are presented in Tables 17a & b and explained subsequently.

Table 17a.

Changes of Cholesterol Fractions

	CFL- (non-adherent)			CFL+ (adherent)			CFL- vs. CFL+
	pre	post	change	pre	post	change (95% CI) *p* one-tailed	diff of change (95% CI) *p* one-tailed
TCH all[a]	225.9 (54.4)	228.4 (56.2)	2.5 NS	223.9 (49.1)	215 (46.0)	-8.9 (-3.8 to -14.0) t(86)=3.5, *p*<0.001	-11.5 (-22.5 to -0.5) t(108)=-2.0, *p*=0.02
≥ 200 mg/dl[b]	247.7 (44.2)	250.1 (46.7)	2.4 NS	241.3 (39.3)	229.7 (39.3)	-11.5 (-5.3 to -17.7) t(66)=3.7, *p*<0.001	-13.9 (-0.1 to -27.8) t(82)=-2.0, *p*=0.02
HDL all[c]	57.2 (16.3)	55.8 (15.5)	-1.3 NS	54.4 (12.9)	55.4 (12.0)	0.9 NS	2.2 (-0.96 to 5.5) t(109)=1.3, *p*=0.08
males[d]	54.5 (15.1)	53.6 (15.2)	-0.8 NS	50.1 (9.1)	52.4 (9.9)	2.3 (0.6 to 4.0) t(61)=2.6, *p*<0.01	3.2 (-0.3 to 6.7) t(78)=1.7, *p*=0.038
TCH/HDL all[e]	4.1 (1.1)	4.2 (1.2)	0.1 NS	4.2 (1.1)	4.0 (1.0)	-0.2 (-0.1 to -0.3) t(86)=3.6, *p*<0.001	-0.3 (-0.06 to -0.6) t(108)=2.4, *p*<0.01
> 4[f]	5.0 (0.8)	5.1 (0.9)	0.1 NS	5.0 (0.8)	4.6 (0.9)	-0.4 (-0.2 to -0.6) t(50)=4.5, *p*<0.001	-0.5 (-0.07 to -0.9) t(61)=2.3, *p*=0.01
LDL all[g]	141.9 (48.7)	145.4 (46.7)	3.5 NS	138.4 (44.5)	133.2 (41.8)	-5.2 (-0.1 to -10) t(86)=2.0, *p*=0.02	-8.7 (1.9 to -19.2) t(108)=1.6, *p*=0.05
males[h]	142.6 (52.1)	148.1 (51.0)	5.5 NS	142.3 (44.5)	136.8 (40.8)	-5.5 (0.8 to -11.9) t(61)=1.7, *p*=0.04	-11.0 (1.7 to -23.8) t(78)=1.7, *p*=0.04

a – for all subjects with valid baseline and follow-up data on TCH; 23 inactive subjects vs. 87 active subjects
b – for all subjects with baseline TCH >=200 mg/dL; 17 inactive subjects vs. 67 active subjects
c - for all subjects with valid baseline and follow-up data on HDL; 24 inactive subjects vs. 87 active subjects
d – for all male subjects; 18 inactive subjects vs. 62 active subjects
e – for all subjects with valid data for TCH & HDL at baseline & follow-up; 23 inactive subjects vs. 87 active subjects
f - for all subjects with baseline TCH/HDL ratio >4; 12 inactive subjects vs. 51 active subjects
g– for all subjects with valid baseline and follow-up data on LDL; 23 inactive subjects vs. 87 active subjects
h – for all male subjects; 18 inactive subjects vs. 62 active subjects

Total Cholesterol

Shapiro-Wilk tests suggested normal distributions at baseline and at follow-up except for a minor deviation in the CFL+ group at baseline. Visual inspection of the histograms and Q-Q plots confirmed the deviation to be minor. Log transformation did marginally improve the normality of the baseline distribution in the CFL+ group, but introduced non-normality in the follow-up distribution. Consequently all analyses were performed as parametric tests on the untransformed raw data. The results for the within- and between-group changes are presented in Table 17a. While TCH remained virtually unchanged in the CFL- group, with a non-significant increase of 2.5 mg/dl from a baseline value of 226 mg/dl, the CFL+ group witnessed a reduction of TCH by 9 mg/dl from a baseline value of 224 mg/dl to 215 mg/dl, which was highly significant with $t(86)=3.5$, $p<0.001$.

Performing the same analysis not including the 12 participants who had reported taking cholesterol lowering medication at baseline did not alter the results substantially, with a non-significant increase of 0.9mg/dl in the CFL- group and a significant decrease of 10.7 mg/dl in the CFL+ group. The latter was highly significant, with $t(78)=4.0$, $p<0.001$.

To investigate whether there was a differential effect of the intervention on those participants whose TCH concentration was equal to or in excess of a 200 mg/dl threshold at baseline, the analysis was repeated for all participants whose baseline TCH values were ≥ 200 mg/dl, regardless of medication status. Again, the CFL- group witnessed a non-significant marginal increase of 2.4 mg/dl from a baseline value of 247.7 mg/dl, whereas the CFL+ group experienced a significant reduction of 11.7 mg/dl from a baseline value of 241.4 mg/dl, with $t(66)=3.7$, $p<0.001$.

Independent-samples t-test was used to test for the between-group difference, performed on the data of all participants irrespective of medication status. The one-tailed t-test returned significance of the between-group difference of change, with $t(108)=-2.0$, $p=0.02$.

These indicate a small, but significant, reduction of TCH in the CFL+ group.

HDL Cholesterol

Shapiro-Wilk tests and visual inspection of the histograms and Q-Q plots suggested normal distributions for the CFL- group at baseline and at follow-up, but strong deviations from normality in the CFL+ group. Log transformation restored normality to the distribution of HDL in the CFL+ group at baseline and at follow-up. To investigate whether the data of female outliers affected the distribution, the normality tests were repeated on the untransformed data for male participants, for whom the data were found to be normally distributed in both CFL groups at baseline and at follow-up.

Since the hypothesis was not gender specific, tests for significance of changes from baseline to follow-up were first performed using paired-samples t-tests on the log-transformed data of all participants, followed by the same tests performed on the raw data. All tests remained

non-significant, for the 1.3 mg/dl reduction from a baseline level of 57.2 mg/dl HDL in the CFL- group, and the 0.9 mg/dl increase in the CFL+ group from a baseline concentration of 54.4 mg/dl.

Paired samples t-tests performed on the male-only data showed a significant increase of HDL of 2.3 mg/dl from a baseline concentration of 50.1 mg/dl in the CFL+ group, with $t(61)=2.6$, $p<0.01$ two-tailed. A small but non-significant reduction of HDL was evident in the CFL- group. Considering the Bonferroni adjustment for additionally testing on gender strata, the independent-samples t-test for significance of the between-group difference of the changes of 3.2 mg/dl approached significance one-tailed, with $t(78)=-1.78$, $p=0.038$ vs. a Bonferroni adjusted significance level of $p=0.025$.

No significance of difference was found between groups when the same analyses were performed excluding participants with a baseline HDL concentration ≥ 60 mg/dl, neither for the male-only subgroup nor for the mixed-gender groups.

Taken together, these data indicate a small and significant increase of HDL in the male CFL+ group.

TCH/HDL ratio

Shapiro-Wilk tests and visual inspection of the histograms and Q-Q plots suggested normal distribution of the TCH/HDL ratio data at baseline and at follow-up in both CFL strata.

Testing for significance of difference between baseline and follow-up showed a non-significant 0.1 increase of the ratio, from 4.1 to 4.2, in the CFL- group. The decrease of the ratio from 4.2 to 4.0 in the CFL+ group was significant, with $t(86)=3.6$, $p<0.001$.

The combined between-group difference of 0.3 was significant two-tailed, with $t(108)=2.4$, $p=0.01$.

Repeating the tests on the data of those participants who had entered the study with a baseline ratio >4, yielded a 0.4 reduction of the ratio in the CFL+ group, which was significant with $t(50)=4.5$, $p<0.001$. The change of ratio observed in the CFL- group remained a non-significant 0.1 increase. The between group difference of 0.5 was significant, two-tailed with $t(61)=2.3$, $p=0.02$.

These results indicate an improvement of TCH-HDL ratio in the CFL+ group.

LDL Cholesterol

Shapiro-Wilk tests and visual inspection of the histograms and Q-Q plots suggested normal distributions for the CFL- group at baseline and at follow-up, but strong deviations from normality in the CFL+ group. Log transformation failed to restore normality in the CFL+ group at baseline and at follow-up. Similarly to the observations of HDL, the distributions were normal in the male-only subgroup of participants. Consequently, parametric tests of

significance for within-group and between-group differences were first performed on the data of all participants, and repeated for the male participants only.

Paired-sample t-tests showed a non-significant increase of 3.5mg/dl of LDL in the CFL- group and a decrease of 5.1 mg/dl in the CFL+ group, which was significant one-tailed, with t(86)=2.0, p=0.02. The between-group difference of 8.6 mg/dl approached one-tailed significance, with t(108)=1.6, p=0.5.

Repeating the test for the males only showed a non-significant 5mg/dl increase of LDL from a baseline concentration of 142 mg/dl in the CFL- group and a significant decrease of equal magnitude in the CFL+ group, with t(61)=1.7, p=0.04 (one-tailed). The between-group difference approached one-tailed significance, given the Bonferroni adjusted significance value of 0.025, with t(78)=1.7, p=0.04.

Taken together, these data suggest a trivial effect on LDL concentration.

Triglycerides

Inspection for normality of the distribution, using Shapiro-Wilk tests and visual inspections of the histograms revealed substantial right-skewing, leading to severe violation of the normality assumption. Log-transformation established normality at baseline and at follow-up in both groups. Therefore, means for TG are presented in Table 17b as geometric means (resulting from antilog of the means of the log-transformed data). For the CFL- group, the within-group factor between geometric means of 0.96, representing an absolute difference of 4.9 mg/dl, is not significant. In the CFL+ group the reduction of TG by a factor of 0.84 represented a negative difference in geometric means of 20.6 mg/dl, which was highly significant two-tailed, with t(86)=3.9 and p<0.001.

To illustrate the effects, expressed in the untransformed data, Table 17b presents the results of the significance tests performed on the the raw data and after log-transformation.

The between group difference, though approaching one-tailed significance, remained non significant, with t(109)=1.3 and t(109)=1.4 for the analysis performed on log-transformed and on raw data respectively, with p=0.08 for both cases.

Table 17b.

Within- and Between-Group changes of Triglycerides

	Significance Tests for log-transformed data				Significance Tests for raw data			
	Baseline[a] Mean (95% CI)	Follow-Up[a] Mean (95% CI)	Δ (factor)	p*	Baseline[b] Mean (95% CI)	Follow-Up[b] Mean (95% CI)	Δ	p**
CFL- N=24	118.7 mg/dl (96.4 - 146.2)	113.8 mg/dl (90.7 – 142.8)	0.96	NS	132.6 mg/dl (106.7 - 158.4)	133.4 mg/dl (94.5 - 172.4)	0.8	NS
CFL+ N=87	132.3 mg/dl (117.8 – 148.6)	111.7 mg/dl (99.3 – 125.6)	0.84	<0.001	155.2 mg/dl (132.9 - 177.5)	131.5 mg/dl (111.7 - 151.4)	-23.7	<0.01
CFL+ vs. CFL-			1.14	0.08		24.5 (-9.8 - 58.8)		0.08

Note:
CFL+ = adherent subjects; CFL- = non-adherent subjects
a: geometric mean resulting from antilog of the t-tests on log-transformed data
b. arithmetic mean
* p-values for paired-samples t-test on log-transformed data
** p-values for paired-samples t-test on raw data

While these observations indicate a triglyceride lowering effect in the CFL+ group, a significant between-group difference could not be confirmed, which is potentially due to the small sample size given the relatively large variance for this lipid parameter.

Interim Summary on Lipids

Summarizing the above, the inspection of intervention effects on the lipid parameters confirms a significant and clinically relevant within- and between-group reduction of TCH and TCH/HDL ratio.

While a borderline significant reduction for LDL was observed, the magnitude of the effect appears to remain trivial and clinically irrelevant. The TG-lowering effect of the intervention, though apparent in the CFL+ group, remains inconclusive as the between-group difference did not reach statistical significance.

The Issue of Intra-Subject Variances

The relatively moderate improvements of lipid parameters have to be viewed in the context of intra-individual variances which were assessed in 61 individuals, randomly selected at baseline for repeated measurement of blood lipids, with a period of 7-10 days between measurements and no change of lifestyle during that period. The results are presented in Table 18 and compared with those of a similar investigation performed by Marcovina et al. in 20 subjects (50% female) [259].

Table 18.

Variability of Lipid Parameters at Baseline

	mean (mg/dL)	CV, %	CV, % Percentiles					
			5	25	50	75	95	Range
TCH Marcovina*	186	6.7	2.2	4.1	5.3	7.9	10.5	1.7 – 11.6
TCH	**220**	**4.7**	**0.3**	**1.4**	**4.2**	**7.0**	**10.3**	**0.3 – 18.1**
TG Marcovina*	98	28.3	6.4	12.2	19.1	29.2	57.6	5.3 – 74.0
TG	**136**	**16.8**	**0**	**8.8**	**15.5**	**23.8**	**34.6**	**0 – 58.6**
LDL Marcovina*	115	9.3	2.5	4.6	8.3	11.4	14.1	2.0 – 15.3
LDL	**137**	**6.8**	**0.8**	**3.2**	**5.8**	**10.0**	**19.0**	**0 – 20.1**
HDL Marcovina*	51	7.6	2.6	4.2	6.5	8.4	12.5	2.2 – 13.7
HDL	**56**	**4.6**	**1.0**	**1.7**	**4.2**	**6.6**	**11.1**	**0 – 11.8**
TCH/HDL	**4.1**	**4.8**	**0.7**	**1.7**	**4.0**	**6.5**	**12.3**	**0.03 – 18.9**

Note:
Values from Marcovina et al (total variability) [259]; values in bold print are values of the ELF sample
TCH: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; CV: coefficient of variation

The variability in the ELF sample is somewhat less severe than the one observed by Marcovina et al. These differences in variability have to be viewed in the context of methodological differences between the studies. Marcovina et al. used 4 blood samplings performed at 2-week intervals between samplings. Considering the results of both investigations, it makes intuitive sense to demarcate parameter changes from baseline to follow-up along an intra-individual threshold of 10% for a change of parameter to be considered clinically relevant. Consequently, participants were dichotomized into successes and failures depending on having or not having improved their baseline lipid values through a 10% reduction (TCH, LDL, TG, TCH/HDL ratio) or increase (HDL) at follow-up.

Two-way contingency table analysis was conducted to evaluate whether the number of participants with a clinically relevant improvement of lipid values was different between the two CFL± groups. The two variables for each table were those of Tables 17a&b (dichotomized to < or ≥ 10% of parameter value at baseline) and CFL status (CFL+ or CFL-). For tables in which none of the expected cell frequencies was less than 5, results of the chi-squared test were accepted for the evaluation of significance of differences. In all other cases the results of Fisher's exact tests were accepted for significance [302].

No significant relations were found between CFL status and change in lipid parameters in excess of 10% of baseline values. , Pearson χ^2 (1, N=115)=9.37, p<0.01. Follow-up logistic regression was conducted to determine the 95% confidence interval of the odds ratio. The results are presented in Table 19.

Table 19.

Odds Ratio (OR) For Improvements Of Lipid Parameters >= 10% Of Baseline Values

	CFL-	CFL+	*p* value (one sided)	OR	95% CI
TCH[a] all	8.7% (2 of 23)	22.9% (20 of 87)	0.1[§]	3.13	0.67 to 14.5
TCH[b] ≥200 mg/dl	11.7% (2 of 17)	26.8% (18 of 67)	0.1[§]	2.75	0.57 to 13.2
HDL[c] all	12.5% (3 of 24)	22.9% (20 of 87)	0.2[$]	2.08	0.56 to 7.7
HDL[d] males	11.1% (2 of 18)	29.0% (18 of 62)	0.1[§]	3.27	0.68 to 15.7
TCH/HDL[e] all	13.0% (3 of 23)	33.3% (29 of 87)	0.05[$]	3.33	0.91 to 12.1
TCH/HDL[f] >4	8.3% (1 of 12)	45.1% (23 of 51)	0.01[§]	9.03	1.08 to 75.2
LDL[g] all	21.7% (5 of 23)	31.0% (27 of 87)	0.38[$]	1.62	0.54 to 4.8
LDL[h] males	22.2% (4 of 18)	29.0% (18 of 62)	0.5[§]	1.43	0.41 to 4.9
TG[i] all	45.8% (11 of 24)	51.7% (45 of 87)	0.6[$]	1.26	0.51 to 3.1

§ Fisher's exact test
$ Pearson's χ^2 test
a – for all subjects with valid baseline and follow-up data on TCH; 23 non-adherent subjects vs. 87 adherent subjects
b – for all subjects with baseline TCH >=200 mg/dL; 17 non-adherent subjects vs. 67 adherent subjects
c - for all subjects with valid baseline and follow-up data on HDL; 24 non-adherent subjects vs. 87 adherent subjects
d – for all male subjects; 18 non-adherent subjects vs. 62 adherent subjects
e – for all subjects with valid data for TCH & HDL at baseline & follow-up; 23 non-adherent subjects vs. 87 adherent subjects
f - for all subjects with baseline TCH/HDL ratio >4; 12 non-adherent subjects vs. 51 adherent subjects
g– for all subjects with valid baseline and follow-up data on LDL; 23 non-adherent subjects vs. 87 adherent subjects
h – for all male subjects; 18 non-adherent subjects vs. 62 adherent subjects
i– for all subjects with valid baseline and follow-up data on TG; 24 non-adherent subjects vs. 87 adherent subjects

The observations presented in Table 19 indicate that the most recognizable intervention effect is a reduction of the TCH/HDL ratio.

Blood Pressure

It has to be noted that no *a priori* hypothesis had been formulated with respect to a potential intervention effect on blood pressure. However, since systolic blood pressure is an integral part of the PROCAM score, an evaluation of the collected data is warranted.

Shapiro-Wilk tests suggested normality of the distributions of systolic and diastolic blood pressure values within both CFL groups of each CFL strata. Visual inspection of the histograms confirmed the normality assumption. Levene's robust test confirmed equality of variances between the CFL± groups of each strata and for systolic and diastolic blood pressure respectively. While the difference in systolic blood pressure between the CFL± groups of the CFL90 and CFL120 strata had approached significance (see Tables 4b & c), there were no significant intra-group changes from baseline to follow-up.

Conversely, with no significant intergroup difference of baseline values for diastolic blood pressure, the latter decreased significantly from baseline to follow-up in all CFL± groups across all CFL strata. However, the changes from baseline to follow-up were not significantly different between the CFL± groups of the CFL strata. The results of the analyses are presented in Table 20.

Table 20.

Absolute changes in blood pressure from baseline to 6-month follow-up in the CFL- and CFL+ groups

		CFL- group (adherent)		CFL+ group (non-adherent)		*p*-value*
		Mean mmHg (SD)	95% CI	Mean mmHg (SD)	95% CI	
CFL90[1]	BPsys	-1.0 (10.0)	-5.2 to 3.2	-1.3 (11.4)	-3.8 to 1.3	0.92
	BPdia	-5.9 (8.8)	-9.7 to -2.2	-3.4 (8.5)	-5.3 to -1.5	0.2
CFL120[2]	BPsys	-0.3 (10.8)	-4.6 to 3.9	-1.5 (11.2)	-4.1 to 0.99	0.61
	BPdia	-5.2 (9.0)	-8.8 to -1.7	-3.5 (8.4)	-5.5 to-1.6	0.37
CFL150[3]	BPsys	0.45 (12.0)	-3.1 to 4.0	-2.5 (10.1)	-5.2 to 0.1	0.17
	BPdia	-2.9 (9.3)	-5.7 to -0.2	-4.8 (7.9)	-6.9 to -2.7	0.27

* p-values were determined by two-tailed t-tests for differences between the groups

1: n=24 for CFL- group (non-adherent); n=80 for CFL+ group (adherent)
2: n=27 for CFL- group (non-adherent); n=77 for CFL+ group (adherent)
3: n=46 for CFL- group (non-adherent); n=58 for CFL+ group (adherent)

Since it is body weight change rather than a change in CRF which affects blood pressure in hypertensive subjects, the effects of a minimum weight loss of 1 kg on blood pressure was investigated. Participants were dichotomized into those having achieved a weight reduction of at least 1 kg vs. those who did not. Since reductions of body weight and blood pressure are clinically relevant specifically for overweight individuals and those with elevated blood pressure levels, the analyses were performed on the 68 participants who had entered the study with a BMI>25 and a systolic and/or diastolic pressure in excess of 129 or 84 mmHg respectively. The categorization of blood pressure follows the current definitions of the American Heart Association (AHA) as the cut-off between normal and elevated blood pressure levels [303].Table 21 presents the results of the paired t-tests and independent-samples t-tests for the within- and between group changes of blood pressure values.

Table 21.

Blood Pressure Change in Weight-Reducing vs. non-Weight-Reducing Overweight Participants With Elevated Blood Pressure At Baseline

	No Weight Loss		Weight Loss		between-groups
	Mean Change (95% CI)	p value*	Mean Change (95% CI)	*p* value*	*p* value**
BPsys[a] (mmHg)	1.2 (-5.2 to 7.7)	0.6	-4.3 (-1.5 to -7.2)	<0.01	0.03
BPdia[b] (mmHg)	-3.4 (-7.2 to 0.4)	0.07	-10.5 (-5.6 to -15.5)	<0.001	0.01

Note: Analyses were performed on overweight participants (BMI>25) with systolic and/or diastolic pressure in excess of 129 or 84 mmHg respectively.
* *p*-values for paired-samples t-test, 2-tailed
** *p*-values were determined by one-tailed t-tests for differences between the groups
a: 16 non-weight-reducing participants vs. 52 weight reducing participants
b: 13 non-weight-reducing participants vs. 21 weight reducing participants

Evidently, there is a significant reduction of blood pressure observable in the overweight participants with elevated pressure at baseline. The median weight loss achieved in this group was 4.4 kg, which correlates well with the approximately 1mmHg reduction of systolic and diastolic pressure, achievable for every 1 kg of loss of body weight reduction [304]. Unexpectedly, though, is the observation that diastolic pressure was reduced to a substantially greater degree than systolic pressure.

Since it has been suggested that the effect of weight reduction on diastolic blood pressure is significantly larger in groups taking antihypertensive drugs than in untreated groups [304], the proportion of individuals having reported taking antihypertensive medications was assessed differentially for the groups of individuals with elevated systolic pressure and those with elevated diastolic pressures. No significant difference was evident between the groups, with 33% vs. 34% of participants with elevated diastolic or elevated systolic pressures respectively reporting being treated for hypertension.

To evaluate whether participants differed significantly across the dichotomized weight-loss groups with respect to changes in blood pressure classification from baseline to follow-up, all participants for whom valid measurements were available (baseline and follow-up) were stratified into one of five categories according to AHA classification [303]:

Category 1 (normal):	systolic < 130 mmHg & diastolic < 85 mmHg
Category 2 (high normal):	systolic 130 – 139 mmHg & diastolic 85 – 89 mmHg
Category 3 (stage 1 HPT):	systolic 140 – 159 mmHg & diastolic 90 – 99 mmHg
Category 4 (stage 2 HPT):	systolic 160 – 179 mmHg & diastolic 100 – 109 mmHg
Category 5 (stage 3 HPT):	systolic ≥ 180 mmHg & diastolic ≥ 110 mmHg

In the CFL90 strata 33.75% and 33.3% of the CFL+ and CFL- groups respectively showed an improvement in blood pressure category from baseline to follow up, with 16.25% and 16.66% respectively showing a deterioration.

While 40.3% (N=57) of the weight-reduced overweight participants with baseline elevated blood pressure had reduced their blood pressure category, 23.8% of the weight-stable participants showed a category drop (N=21). This difference, though approaching significance, remained non significant (one-tailed), with z=-1.35, p=0.088.

PROCAM Risk Score

Inspection for normality of the distribution, using Shapiro-Wilk tests and visual inspections of the histograms, revealed substantial positive skewing, leading to a severe violation of the normality assumption. Log-transformation established normality at baseline and at follow-up in both groups, whereas restriction of the analysis to the male-only raw data did not. Therefore, means for the PROCAM score are presented in Table 22a as geometric means

(resulting from antilog of the means of the log-transformed data). For the CFL- group, the within-group factor between geometric means of 1.08 is not significant. In the CFL+ group the risk reduction by a factor of 0.79 represented a negative difference in geometric means which was highly significant two-tailed, with t(55)=4.08 and p<0.001.

To illustrate the effects, expressed in the untransformed data, Table 22a presents the results of the significance tests performed on the log-transformed and on the raw data. In the evaluation of the raw data, the significance is preserved, though attenuated.

Table 22b and Figure 13 show the mean values of the relative change of the scores, expressed as percentage change of the scores, for both CFL groups in each strata. While CFL- subjects of the CFL90 strata showed a mean 16.6% relative increase in the score, the CFL+ subjects of that strata decreased their score on average by 14.7%.

These results indicate a significant effect of the intervention on cardiovascular risk factors as expressed in the PROCAM score.

Table 22a:

PROCAM Risk Score: Within- And Between Group Differences From Baseline To Follow-Up

	Significance Tests for log-transformed data				Significance Tests for raw data			
	Baseline[a] (95% CI)	Follow-Up[a] (95% CI)	Δ (factor)	p^*	Baseline[b] (95% CI)	Follow-Up[b] (95% CI)	Δ	p^{**}
CFL- [c] N=15	4.36 (2.92 to 6.5)	4.73 (2.95 – 7.59)	1.08	NS	5.72 (2.8 – 8.6)	6.5 (3.5 – 9.5)	0.78	NS
CFL+ [c] N=56	5.24 (4.31 - 6.38)	4.13 (3.37 – 5.06)	0.79	<0.001	6.8 (5.3 – 8.2)	5.5 (4.2 – 6.7)	-1.3	<0.01
Between -Group			1.36 (1.09 – 1.73)	<0.01			2.08 (0.33 – 3.79)	<0.05

a: geometric mean resulting from antilog of the t-tests on log-transformed data
b. arithmetic mean
c: CFL- = non-adherent; CFL+ = adherent
* p-values (one-tailed) for paired-samples t-test on log-transformed data
** p-values (one-tailed) for paired-samples t-test on raw data

Table 22b

Relative Change Of PROCAM Risk Score

	% - Change			
	CFL-	CFL+	Δ, p-value*	95% CI
CFL90 (N=15/56)[a]	16.6	-14.7	31.3 (p<0.01)	10.2 to 52.4
CFL120 (N=18/53)[b]	13.1	-15.2	28.3 (p<0.01)	8.4 to 48.2
CFL150 (N=30/41)[c]	8.1	-19.8	27.9 (p<0.01)	10.6 to 45.1

* p-values (one-tailed)
a: n=15 for CFL- group (non-adherent); n=56 for CFL+ group (adherent)
b: n=18 for CFL- group (non-adherent); n=53 for CFL+ group (adherent)
c: n=30 for CFL- group (non-adherent); n=41 for CFL+ group (adherent)

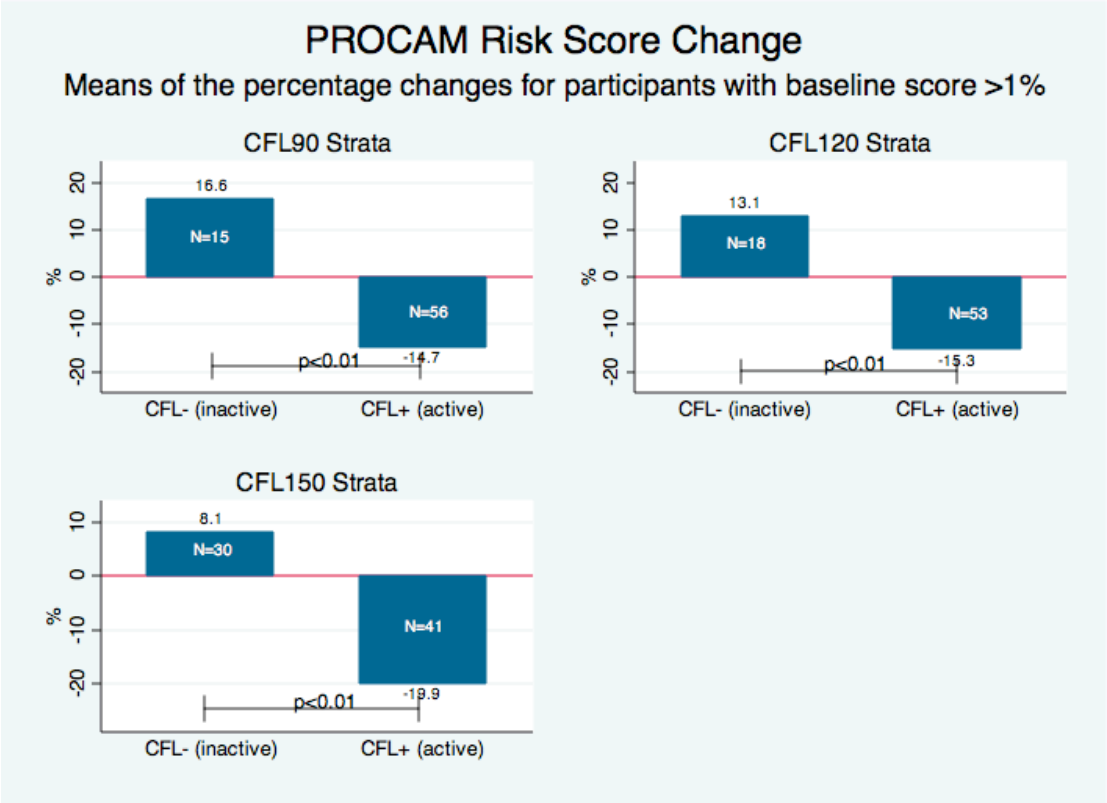

***Figure 13*. Relative Change of PROCAM Risk Scores**

Two-way contingency table analysis was conducted to evaluate whether the number of participants with a relative reduction of PROCAM risk score of ≥10% was different between the CFL± groups. For all tables, the expected cell frequencies were in excess of 5. Therefore the results of the chi-squared tests were accepted for the evaluation of significance of differences [302].

Follow-up logistic regression was conducted to determine the 95% confidence interval of the odds ratio. The results are presented in Table 23.

Table 23

Odds Ratio (OR) For A Relative Decrease Of PROCAM Risk Score ≥10% (CFL+ vs. CFL-) by CFL strata

	CFL- (non-adherent)	CFL+ (adherent)	*p* value	OR	95% CI
CFL90[a]	20% (3 of 15)	58.9% (33 of 56)	*p*<0.01	5.7	1.4 to 22.6
CFL120[b]	22.2% (4 of 18	60.3% (32 of 53)	*p*<0.01	5.3	1.5 to 18.4
CFL150[c]	30% (9 of 30)	65.8% (27 of 41)	*p*<0.01	4.5	1.6 to 12.3

Note:
for all subjects with baseline PROCAM risk score >1%
CFL90: criterion active duration = 3 months; CFL120: criterion active duration = 4 months; CFL150: criterion active duration = 5 months
PROCAM: Prospective Cardiovascular Münster Study
a: 15 non-adherent subjects vs. 56 adherent subjects; **b:** 18 non-adherent subjects vs. 53 adherent subjects;
c: 30 non-adherent subjects vs. 41 adherent subjects;

Intervention Effects on the Overweight Participants

Sedentary, overweight individuals are the primary target group of the studied intervention. Hence, it is informative to evaluate whether the intervention had affected the outcome parameters of this group and what was the magnitude of these effects. Table 24 and Figure 14 present the intervention effects on all parameters for which within- and between-group differences have been found to be significant and which had been hypothesized to correlate directly with adherence to the exercise protocol. The data are analyzed for all participants with a BMI >25 at baseline and irrespective of the outcome parameters' values at baseline.

Table 24.

Main Intervention Effects On The Overweight & Obese Participants

	Mean change from baseline to follow-up		Mean change between-group difference		
	CFL- (non-adherent)	CFL+ (adherent)	absolute	p value	95% CI
VO_2peak[a] ml/kg/min	-0.59 (*p*=0.2)	3.72 (*p*<0.001)	4.3	*p*<0.001	2.55 to 6.08
weight[b] kg	-1.5 (*p*<0.05)	-4.3 (*p*<0.001)	2.8	*p*<0.05	0.6 to 4.9
BMI[b] kg/m^2	-0.45 (*p*<0.05)	-1.4 (*p*<0.001)	0.95	*p*<0.01	0.25 to 1.6
TCH/HDL[c]	+0.13 (*p*=0.3)	-0.23 (*p*<0.001)	0.37	*p*<0.01	0.1 to 0.6
PROCAM[d] score % absolute	+0.68 (*p*=0.1)	-0.8 (*p*<0.01)	1.48	*p*<0.05	0.28 to 2.68

Note:
a: 22 non-adherent subjects vs. 60 adherent subjects; **b:** 24 non-adherent subjects vs. 73 adherent subjects;
c: 21 non-adherent subjects vs. 71 adherent subjects; **d**: 19 non-adherent subjects vs. 68 adherent subjects

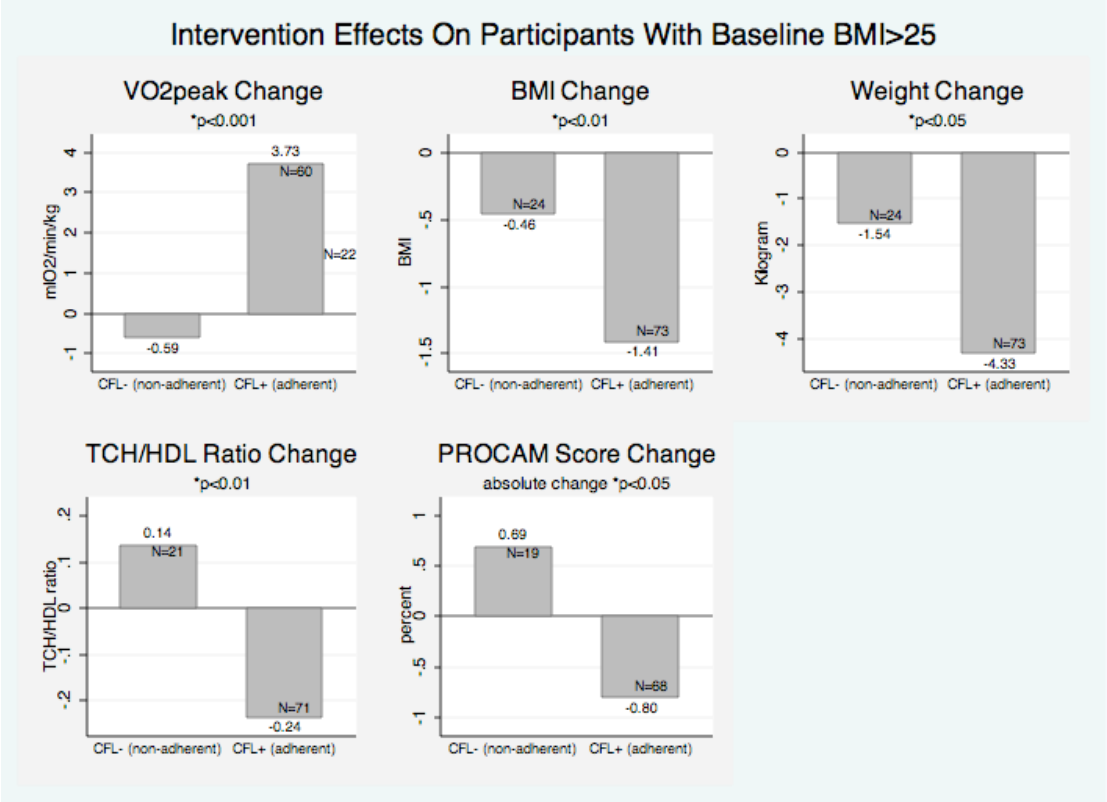

Figure 14. Main Intervention Effects On Overweight Participants

**p*-values for difference between CFL groups

PEER COMPARISON OF THE INTERVENTION

Since optimizing intervention efficiency was an objective of this study, comparisons with trials using similar exercise curricula is warranted.

To this end, the ELF intervention effects were compared to the results published for an exercise intervention in 21 overweight, apparently healthy men [106]. The men had been studied before and after a 12 weeks exercise intervention (no dietary intervention), which consisted of thrice-weekly supervised exercise sessions of 40-60 minutes of moderate intensity treadmill walking & jogging. This study of Miyaki et al. was chosen for its close similarity of key aspects with the ELF intervention, specifically

- the similarity of baseline parameters as outlined in Table 25,
- the 12-weeks duration of the intervention which equals the 12 weeks duration aspect of the CFL90 group
- assessment of VO_2peak by ergospirometrie
- availability of data on a *per subject* basis

Table 25 presents the comparison of baseline values between the two study populations. Since one of the men in the study of Miyaki et al. had a baseline BMI less than 25, the values of this subject were not considered in the analyses.

The significantly smaller height and weight and higher body fat content, with concomitant non-significant difference in BMI, reflect the fact that the sample of Miyaki et al. consisted of Japanese subjects. Compared to Europeans, Asians have a higher body fat content at the same BMI value [305, 306]. VO_2peak values were only available as a group mean, which prevented analyses of VO_2peak per kg of lean body mass.

Table 25:

Baseline Comparison Of Overweight ELF Men (BMI>25) With The Male Study Population Of Miyaki et al.

	Miyaki et al. N=20	ELF study N=73	p-value for difference
Age	49.3 (9.66)	50.6 (8.06)	0.59
Height (cm)	169 (7.2)	178 (6.6)	<0.001
Weight (kg)	87.4 (12.1)	94.1 (11.9)	<0.001
BMI	30.3 (3.2)	29.5 (3.0)	0.31
Body Fat (%)	32.6 (3.7)	26.4 (4.06)	<0.001
VO_2peak ml/kg/min	29.0 (4.12)	33.9 (7.03)	<0.01
TCH mg/dl	237 (45.8)	224 (54.4)	0.29
HDL mg/dl	51 (15.8)	50 (10.8)	0.67
TCH/HDL ratio	4.87 (1.47)	4.58 (1.1)	0.42

Figure 15 compares the changes in vital signs achieved in both study samples.

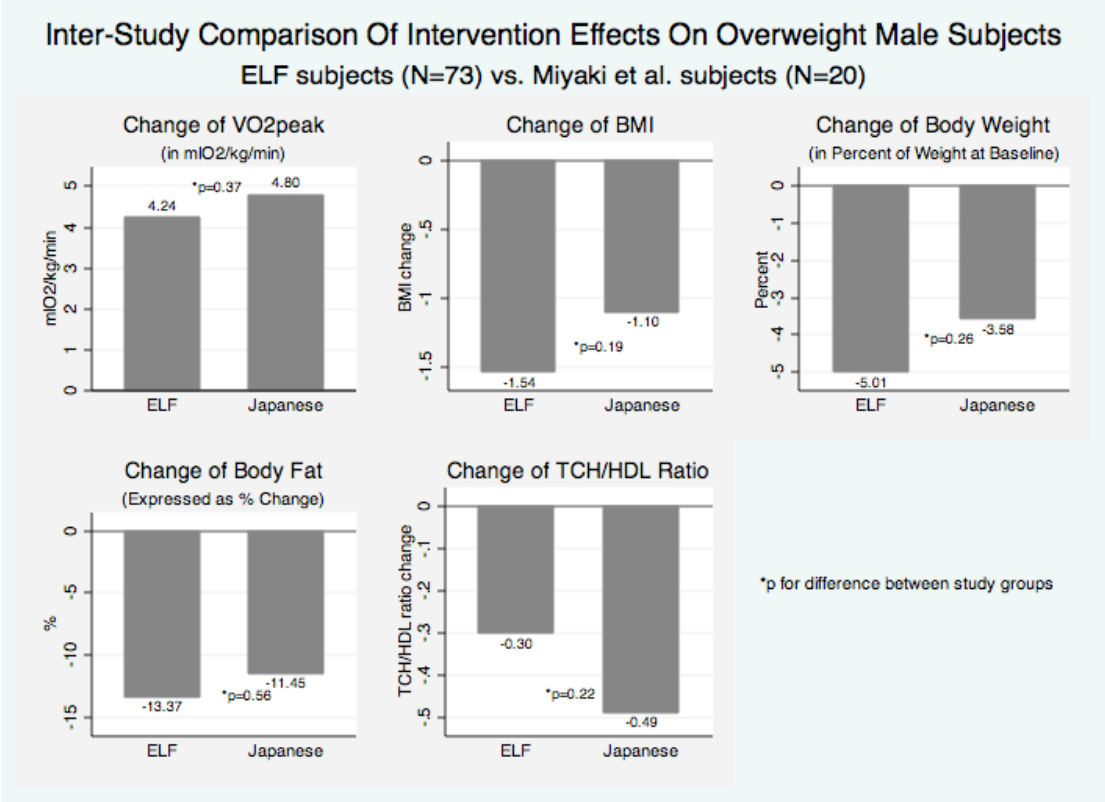

***Figure 15*. Comparison of the ELF sample with the sample of Miyaki et al**

No significant differences were found between the two study samples.

The context and implications of these observations are discussed in the following section.

DISCUSSION

BASELINE COMPARISONS

Efforts to detect true between-group differences and to avoid chance findings

This study investigated the effects of a “minimally invasive” self-monitored exercise protocol on adherence to a physical activity intervention, which was designed to improve various parameters of cardiovascular health in a predominantly sedentary and overweight, but otherwise apparently healthy population of working adults. As the intervention was carried out under the evidence-based *a priori* assumption of tangible health benefits accruing to adherent participants, the study had been designed to test its hypotheses through comparison of adherent with non-adherent subjects rather than through intention-to-treat analyses based on a randomized controlled design. This given study design necessitates a thorough investigation into potential baseline differences between the two comparison groups, which had been stratified according to their adherence status in participants who did or did not meet the pre-defined adherence criteria of latency of self-reporting, volume and duration of reported exercise.

Any systematic difference between these two groups at baseline potentially affects the interpretation of the outcome analyses. Similarly, chance findings of significant baseline differences, when there are actually none, may equally flaw the interpretation of study results. The severity of these issues had been highlighted 30 years ago by Lee *et al.* who simulated a clinical trial randomizing the clinical records of 1073 consecutive cardiac patients into two mock treatment groups [307]. As expected, the outcome analysis showed no significant difference in survival between the groups. However, post hoc stratification of the patients into subgroups according to variables which affect prognosis (the number of diseased coronary vessels) yielded significant differences in survival between the two mock treatments. In a real intervention, this obvious chance finding might have been interpreted as a treatment effect becoming clinically relevant in the more severely ill patients.

Correspondingly, a baseline difference between the two ELF participant groups, may theoretically (a) have systematically moderated a true intervention effect such that no significant between-group difference would have been observed or may (b) have systematically affected the baseline-to-follow up progression of parameter values to suggest an intervention effect when there was none.

Given these considerations the investigation into potential baseline differences was conducted with a bias towards avoiding type II errors rather than type I errors. Hence, the type I error-minimizing Bonferroni corrections were applied judiciously, that is, no Bonferroni corrections were used across the 13 investigated variables, which can also not be considered as truly independent variables, a prerequisite for correct use of the correction. However, the investigation into gender specific baseline differences warranted a Bonferroni correction, as this stratification was not based on *a priori* hypotheses, but arose merely from the need to investigate whether the different proportions of female CFL± group members were a potential source of the differences in body weight observed between the two groups at baseline. This line of investigation is justified for parameters for which gender-specific differences are known to exist, such as VO_2peak, body weight, body fat, lipids and PROCAM risk score.

Owing to the relatively small comparison groups, effect size calculations were carried out with the view that, when a relatively large effect size (for between-group baseline differences) coincides with the finding of no significance, the sample size may in itself affect the interpretation. In this context, it is important to conduct the analyses to be as sensitive as possible for the detection of significant differences. While the applied independent-samples t-tests are known to be relatively robust to small violations of the assumptions of normality of the distributions and equality of variance, data were transformed for closer conformation with the normality assumption in all instances where the raw data (a) showed clear violations of this assumption through pronounced skewness, and (b) t-tests did not return significance of between-group differences. The rationale being, that the most likely effect of these violations is a loss of power to detect a true difference, while type 1 errors are unlikely [308].

The preferred transformation was the log-transformation, the anti-log of which yields interpretable results, whereas all other transformations may simply be used as a test to indicate significance.

Given the aforementioned considerations, the baseline evaluations confirmed that there were no differences between the CFL+ and CFL- groups which my have systematically affected the interpretation of the follow-up analyses. While the proportion of females was higher in the CFL+ group than in the CFL- group, with 30% vs. 21% respectively, this difference was not significant. Due to it, however, the between-group difference in body weight of 6.3 kg at baseline approached significance, with the CFL+ group being lighter than the CFL- group. Since this difference was not reflected in BMI it can be ascribed to the large difference of 14 kg between the female-only CFL groups. The small sample size of the female CFL- group however defies a meaningful interpretation of this difference.

There is some published evidence to suggest, that BMI correlates inversely with adherence to exercise interventions [309, 310]. While the mean BMI in the CFL- group was 1.2 units higher than that in the CFL+ group (29.8 and 28.6 for the CFL- and CFL+ groups respectively), this difference remained not significant. The distribution of the data was equally normal in both groups and no transformation achieved improvement of the distribution to the extent that t-test statistics would have increased, thereby indicating increased power. Hence, no correlation between BMI and adherence can be confirmed in this sample, which may be due to the fact that mean BMI remained below 30, and very few participants had entered the intervention at a BMI sufficiently high to affect adherence.

Worthy of note is the difference in PROCAM score, which approached significance in the male subgroup. While the overall score remains substantially below the 10% cut-off, which is used to differentiate the low-risk from the moderate-risk individual, the achievable score of 1% for a reference 50-year old male remains substantially lower than the observed group mean.

That the female strata displayed a substantially lower risk level than the male strata reflects published evidence of CVD risk being dramatically lower in pre- and perimenopausal women compared to their age-matched male peers.

Owing to the small sample sizes and the very low PROCAM risk scores for the female subgroups, the results of the t-tests performed on the log-transformed data of these groups defy any meaningful interpretation.

Taken together, these results suggest that there were no significant differences in PROCAM risk scores at baseline between the CFL groups. The difference in scores observed in the male subgroup, though approaching significance, is to be considered clinically not relevant, as the scores remained within the lower half of the low-risk bandwidth of the score. Hence, the assumption of baseline differences, which affect the interpretation of intervention effects on the groups at follow-up, can be rejected. This observation holds equally true for the baseline differences presented in tables 3c&d for the CFL120 and CFL150 strata respectively.

Effort to compare the ELF sample with relevant underlying populations

With the given recruitment strategy and the potential selection biases engaged by it, it was unlikely for the study population to be representative of the general population.

First, there is bias related to the self-selection process. Owing to this volunteer bias, the more health-conscious individuals of a population are almost inevitably over-represented in the study population [311, 312]. This bias potentially shifts the distribution of health related vital signs within the study population towards the healthier end of the spectrum compared with the general population. However, there is evidence to the fact that this bias does not necessarily generate a study population, whose health parameters substantially and significantly differ from those of the general population. An attempt to quantify the differences in total cholesterol and blood pressure levels between men who self-enrolled into a 12-months exercise program for the prevention of CVD and those of the general population from which the subjects had been drawn, did not show any significant differences between the volunteers and the general population [313].

Second, there is bias related to the population of employed individuals, from which the study population was drawn. McMichael had suggested, that to be employable an individual must be relatively healthy and that therefore, the workforce of an industrial enterprise without significant health hazards presents a lower mortality rate than that which is observed in the general population [314]. The author had termed this effect the “healthy worker effect” (HWE), which he had observed in the context of studying the vocation-specific mortality rates in rubber workers. These observations may extend to parameters of morbidity and to vital signs, skewing their distribution towards the healthier end of the population spectrum.

As unavoidable as this may be in self-selected samples of intervention participants, it is probably of negligible effect when extrapolating the intervention results to future interventions using similar protocols in different populations, as the latter will similarly be affected by volunteer bias. Hence, the suggestion has been made to explain meaningful distinctions between the sample and the general populations rather than to be overly concerned with the healthy worker effect [315].

To investigate the possible extent of these biases’ effect on the ELF sample, an attempt was made to compare its baseline values with those in a representative population sample, drawn under the MONICA investigation into correlates and trends of cardiovascular health [233].

For this comparison, the German MONICA population of the urban Augsburg reporting unit was chosen as the one for which cross-sectional data were available and which most closely resembled the urban South-West German population from which the ELF sample had been drawn. As expected from the preceding discussion, the ELF sample tended to represent a slightly healthier spectrum of the population. Despite a significantly and substantially elevated BMI (28.7 and 29.3 for the male and female ELF samples respectively), which was located towards the upper end of the overweight range, the significantly lower concentration of TCH

and the significantly reduced TCH/HDL ratio are indicative of a better health status.

Blood pressure values were not significantly different between the samples. This comparison, however, has to be viewed in the context of the regional (Bavarian vs. Baden-Wuerttemberg locations) and temporal (mid-nineties vs. 2009) distance between the two sampling processes. Therefore, the comparison of the ELF sample data with the MONICA population was cross-checked with the more recent data published for the German Microcensus conducted in 2005. This comparison confirms the conclusion drawn from the comparison with the MONICA sample, namely that the ELF sample presented with a substantially higher BMI than the general population, and with a marginally better lipid profile than that of a comparable age cohort of the mid-nineties.

One of the study objectives was to enroll sedentary adults and to investigate the effect of the intervention on cardiorespiratory fitness as the main outcome parameter, owing to its strong inverse correlation with cardiovascular risk as discussed in the preceding sections. Since no published data from cross-sectional evaluations of German reference populations could be identified, the criteria for the selection of acceptable representative study populations were extended to include those of similar ethnic background, age bracket, health status and measurement protocol for the assessment of VO_2peak. The Finnish Kuopio Ischaemic Heart Disease Risk Factor Study (KIHDS) was chosen for its close similarity to the specified parameters [236] and for its purpose of investigating the prognostic value of VO_2peak for cardiovascular disease incidence.

While the primary focus of this comparison was on the VO_2peak values, it incidentally provided for a further comparison of selected lipid parameters.

Again, The ELF men were significantly more overweight than the Finnish male cohort, with a BMI of 28.7 vs. 26.6 and 27.1 in the Finnish healthy and unhealthy men respectively. The ELF men were marginally but significantly fitter than the healthy Finnish cohort, with a difference in VO_2peak of 2.1 ml/kg/min, and substantially and significantly fitter than the unhealthy Finnish men, with a VO_2peak difference in excess of 2 MET (7.3 ml/kg/min). In this Finnish population VO_2peak was found to decrease non-fatal and fatal cardiac events by 17-29% and by 28-51% respectively for every one MET increment. Hence, the difference to the unhealthy Finnish men constitutes a clinically relevant difference, given the observation by others that every MET increase in aerobic capacity may confer a 12% reduction of cardiovascular mortality risk [316]. This observation reinforces the importance of CRF as a clinically powerful, relevant, and modifiable risk factor for CVD.

The comparison with the KIHDS men suggests, that the ELF sample presents with a level of CRF which is typical for a healthy but sedentary population, and which is substantially better than that of a diseased population.

Any reasoning on the observations of similar values for TCH and HDL, significantly lower concentrations of LDL and significantly higher concentrations of TG among the ELF men,

would be speculative at best and may well be a chance finding. While that may apply *mutatis mutandis* to the differences in blood pressure values, with systolic pressures being higher and diastolic pressures being lower in the ELF men, a closer look at the differences between the Finnish and the MONICA populations is illustrative of potential underlying population differences.

The reason for this difference possibly reflects a greater prevalence of hypertension in the German compared to the Finnish population. 38.2% of the male MONICA subjects had a history of hypertension, whereas the equivalent figure for the KIHDS population was reported with 24%. Moreover, 8.5% of the male MONICA subjects had systolic and diastolic blood pressure value of >= 160 mmHg or DBP >= 95 mmHg respectively and had been told about high blood pressure previously but did not take any medication. Another 10.5% had systolic and diastolic blood pressure values of >= 160 mmHg or DBP >= 95 mmHg respectively, did not take any medication and had never been told about having high blood pressure. Hence, the non-significant differences in blood pressure values between the ELF and the MONICA samples, with both being significantly different from the Finnish population, may reflect underlying population differences rather than specific differences between the ELF and the KIHDS population.

Taken together, the baseline comparisons suggest that the ELF population probably represents a more health conscious strata of the population, which nevertheless displays the risk factors which are typical for a predominantly sedentary lifestyle, namely moderate CRF, pronounced overweight and concomitant lipid and haemodynamic profiles in the sub-optimal range, all of which adds up to a low to moderate CVD risk as evidenced by a relatively low, but far from optimal PROCAM risk score.

HYPOTHESES TESTING

Adherence

As the hypothesized 75% adherence is within the confidence interval of the proportion of adherent subjects, the data support hypothesis 1.

The proportion of 76% of subjects completing the study as actively self-monitoring participants needs to be discussed in the context of adherence. Over the longer term, the degree of adherence is inevitably subject to fluctuations, owing to disruptive external and internal (seasonal, occupational, health and other) constraints. It is essential to rescue the health habit over any hiatus that may be caused by these external factors. Self-monitoring is the essential tool to achieve this. Hence, active self-monitoring, if suitably defined along the dimensions of latency, volume and duration will serve as an important tool to maintain adherence.

The three aspects defining active self-monitoring in this study were:

- *latency* of last reporting event not exceeding 7 days to follow-up assessment
- *duration* of continuously recorded self-monitoring of 12 weeks
- *volume* of PA of weekly 60 minutes of HIT or more

As discussed in the introductory sections, these minimum requirements had been developed from the evidence-based expectation that (a) measurable health benefits would accrue to the adherent subjects, and that (b) these benefits would emerge as statistically significant differences between CFL+ und CFL- groups.

The latency aspect of this definition differentiates it from those adherence definitions, which are exclusively based on any combination of percentages of volume, of duration or of attendance. It provides an answer to the question, what proportion of study participants currently adheres to the PA protocol and has done so for durations and at PA volumes, which are expected to yield tangible health benefits. Hence, the latency aspect is essential for determining how successful an intervention has been at releasing its participants with a modified health habit. With a view to continuous interventions, the latency aspect is essential in recognizing individuals who are at risk of drop-out or whose adherence begins to decay. In this context latency assessment provides the means to direct attention to those individuals whose current adherence status warrants additional motivational efforts.

Extending the duration component without modifying the latency and volume components (as done by defining the CFL120 and CFL150 status) does not result in a reduction of adherent subjects, as the main aspect of adherence is the presence of an operant CFL at the time of assessment. Rather does it differentiate adherent subjects into different strata of duration of continuous adherence history. It is important to keep this aspect in mind when interpreting the results of comparative evaluations of the measured parameters of physical fitness and biochemistry between the strata. The progressively smaller intra-strata differences between CFL- and CFL+ group-means of parameter values (VO2peak, body weight, BMI body fat and lipids) are a result of these improvements being measurably evident in the adherent individual after 12 weeks of changed PA levels. Grouping some of these individuals into CFL- groups in the CFL120 and CFL150 strata inevitably leads to a progressive attenuation of the differences of group means. Hence, the latter must not be considered a decay of intervention effect over time, but a merely statistics related artifact.

As I have elaborated in the introductory sections, the absence of adherence standards complicates inter-study comparisons. In this study, the term adherence does not relate to the volume or duration of PA, but to the presence of an operant cognitively controlled feedback cycle at the end of a 6-months observation period. This constitutes a small, but substantially different way of defining adherence, which emerges from the theory and model underlying this intervention strategy.

Hence, comparisons with published adherence rates are difficult, if not meaningless. Adherence in time-limited trials simply identifies the dose of PA medicine taken by the participants. It has helped us to discover the dose-response relationship between the medicine, that is PA, and health. With a view to the acknowledged decay of taking the medicine, we now need to work out how to prevent this decay in the first place.

Therefore it is far more instructive to see whether the intervention protocol, which emphasizes monitored self-monitoring of a minimally invasive curriculum with substantial inter-individual differences of PA intensity and volume, has demonstrated the potential to produce significant and clinically relevant improvements of objectively measurable health parameters, such as the ones examined in this study.

Namely, that instituting and maintaining a health enhancing physical activity habit critically depends on reactivating physical activity as the effector in a feedback loop of human energy homeostasis through cognitive control. The latter being required as a substitute for the autonomous control mechanisms, which have been imprinted through evolution to balance human energy intake with the PA cost for the acquisition of food and its energy density. The massive disruption of these autonomous control mechanisms, which is typical for modern human societies, has emerged as a major pathogen to the human phenotype. In this context, this trial may represent the beginning of a new intervention paradigm, the essence of which is continuity of the PA intervention through facilitated and monitored self-monitoring.

Support for this view comes from a recent meta-analysis of 122 lifestyle change interventions, in which the combination of self-monitoring with one or more other theory based techniques had a substantially and significantly larger effect on the outcome parameters than interventions which lacked self-monitoring techniques [317].

Simple techniques, such as frequent self-weighing in weight loss trials, have shown to substantially improve target outcomes, with frequently self-weighing participants achieving double the weight loss compared to their not self-monitoring intervention peers [318].

The worksite intervention of Atlantis *et al*. had used a very similar intervention protocol (minimum 3x20 minutes of moderate to high intensity aerobic training), duration (24 weeks) and setting (worksite), but did dot deploy any self-monitoring technique [235]. Given the discussed considerations about the correlation of the latter with adherence and outcome, it is tempting to speculate that the substantially and significantly better adherence in the ELF trial (76% vs. 58%) may be due to the technique of self-monitoring. However, with 73% of the Atlantis intervention participants being shift workers, the work environment with its commensurate time constraints may also have affected the adherence rate.

Extension of the ELF trial, in terms of duration and study populations, will help to substantiate (a) the underlying strategy's ability to substantially enhance the prevalence of HEPA habits within target populations, and (b) how to optimize this strategy for maximum public health benefit.

Maximal Oxygen Uptake

The results favor the hypothesis that the group of participants with an operant controlled feedback loop, as evidenced by their active self-monitoring of PA, improved cardiopulmonary fitness significantly and to a clinically relevant extent, whereas lack of self-monitoring correlates with lack of change in cardiopulmonary fitness. The difference between the two groups is significant and clinically relevant.

The Phenomenon of the Highly Motivated Outliers

The phenomenon of few highly motivated intervention participants skewing the outcome parameters is an observation reported in published evidence. In a comparable work-site intervention of 24 weeks duration, Atlantis et al. report the case of one highly motivated female participant who reduced her baseline BMI of 40 by 12.6 kg/m2 and her body weight by 33.7 Kg [235], which makes that individual's intervention effect comparable to that of the male subject in this study. Similar observations have been published for an investigation into the inter-individual differences in weight change resulting from a controlled 12-week exercise intervention in a group of 35 overweight and obese subjects [212]. While the reported mean weight loss was 3.7 Kg, one individual had reduced his weight by 14.7 Kg or 3.4 SD above the group mean.

These observations suggest that the highly motivated individual, who "super-achieves" intervention targets, is a common phenomenon, which needs to be accounted for when presenting the data. Data interpretation becomes problematic when the analyses with and without the overachieving outliers are contradictory in significance. This was not the case in the ELF population where within- and between-group differences remained significant, though moderately attenuated, when analyses were conducted with and without the outliers.

Relevance of the intervention effect on cardiorespiratory fitness

The data support the hypothesis that actively self-monitoring subjects witness a significant increase of maximal oxygen consumption capacity over their non-self-monitoring peers.

Baseline value of VO2peak of this study population places it approximately into the 50th percentile of published reference populations [238]. This leaves substantial room for improvement, which promises an equally substantial gain in health benefits.

In the Finnish study population cardiorespiratory fitness (expressed in VO_2peak) emerged as the strongest predictor of non-fatal CVD events over the 13.7-year median follow-up. At 1-MET increments of VO2peak the risk of non-fatal and fatal coronary events was reduced by a constant proportion, regardless of existing CVD, and with a threshold effect observed between very low and moderate fitness levels. Similar reductions of disease risk have been observed in other investigations of mixed-gender populations which confirmed the risk-reducing effect of cardiorespiratory fitness similarly in men and women [319]. Hence, the

increase of VO2peak observed in this study population constitutes a significant and clinically relevant effect.

With a view to the concurrent weight losses observed in the CFL+ subjects (discussed in the succeeding section), it was necessary to investigate whether the observed increase in VO_2peak relative to body weight was a true increase of CRF or simply an arithmetic artifact. That is, if weight loss is primarily achieved through reduction in body fat, with concomitant preservation of muscle mass, the increase in VO_2peak does not necessarily reflect an improvement of the oxygen uptake dynamics in the working muscle tissues. This is an important caveat when evaluating concurrent dietary and PA intervention effects, as it has been shown that weight loss alone does not improve fat oxidation efficiency in working muscle mitochondria, but only exercise does [320].

However, Table 8 and Figure 6 demonstrate that VO_2peak improved significantly relative to BCM, thereby confirming a net increase in cardiorespiratory exercise capacity.

Irrespective of the goal of improving CRF, PA in itself is a correlate of health worth monitoring.

Of the 4,456 young females of the U.S. Growing Up Today Study (GUTS) who were aged 14-22 at baseline, 24% and 54% reported efforts to maintain or to lose weight respectively [321]. Despite these efforts a mean weight gain of 3.3 kg was observed over the 4-years follow-up from 2001 to 2005. Of the various weight management strategies, which were evaluated, only the combination of limiting portion sizes and exercising at least 5 times/week emerged as a significantly protective strategy against weight gain. In this context, self-monitoring of PA is an essential tool to maintain PA levels, the eventual decay of which otherwise precipitate weight (re-)gain.

Specifically, the post-intervention, weight-reduced individual is vulnerable to weight re-gain. It has been shown that the maintenance of body weight at approximately 10% below a pre-weight-loss status leads to a decrease of energy metabolism, specifically in low-intensity activities, below what would be predicted by weight change alone [322]. Hence, the maintenance of higher levels of PA, specifically at higher intensity, becomes a *sine qua non* for successful maintenance of a reduced body weight.

More importantly, recent results from aging research suggest that PA and its related energy expenditure not only strongly correlate with longevity, but that PA may in itself be regarded as a biomarker for senescence and death [323]. So has it been proposed that timed exercise may contribute to the stabilization and improvement of the circadian rhythm in aging organisms, thereby delaying senescence and death [324].

Indirect evidence for the association of PA with longevity comes from population studies of the correlation between PA and older-age associated disease. In a large prospective follow up of 28,842 men and 30,336 women over a 30 years period from 1972 to 2002, PA was strongly and inversely correlated with the risk of heart failure (HF) [325]. In this study sample,

which had been stratified in 1982 according to the WHO MONICA protocol, the protective effect of PA was evident across the entire range of BMI values.

Obviously, self-monitoring of this supremely modifiable biomarker not only makes sense, but not to avail oneself of the leverage it provides for increasing health and life span, does not make sense at all.

Given these observations, the improvement of CRF in a predominantly sedentary population such as ours, and the introduction of a self-monitoring tool for improving the biomarker PA, is of primary public health value.

Unsurprisingly, the U.S. government's "Healthy People 2010" initiative has recognized PA as the top health indicator, followed by overweight/obesity, in its list of the 10 leading health indicators [288]. These indicators and their prioritized sequence had been chosen to (a) reflect the government's major public health concerns and (b) highlight their relevance in improving public health.

If translatable into a larger public health context, the improvements of CRF achieved in the ELF study sample, and the self-monitoring tool developed to facilitate this improvement, could provide a significant contribution to public health and the reduction of CVD.

Parameters Of Body Weight Status

It needs to be kept in mind that the primary objective of this intervention was the activation of an operant CFL, the primary purpose of which was to increase cardiorespiratory fitness. While the individualized exercise prescription to achieve this goal was set at a minimum of 3x20 minutes of moderate- to high-intensity interval training per week, subjects were free to exercise in excess of this minimum requirement. The hypothesized and expected weight-loss of 2.5 kg had been based on the assumption that the actual time spent exercising would be close to the required minimum for most of the active participants.

The median of the actual time spent exercising, however, was ~2.5 times the 60' minimum requirement. The same factor applied to the hypothesized weight loss would translate into a 6.2 kg reduction of body weight, which is higher than the mean of 4.6 kg achieved in the CFL150 strata. However, this difference needs to viewed in context. Firstly, the applied method of reporting the time spent exercising did not provide for a quantification of its calorific equivalent, as the intensity at which exercise was performed could not be captured. Secondly, substantial inter-individual differences in weight response to exercise are known to exist, which span the range from compensatory dietary increase in caloric intake to no dietary compensation at all [212].

Nonetheless, the observed odds ratio of 8 (CFL+ vs. CFL- group) in the CFL90 strata for reducing body weight by ≥5% vs. reductions of less than 5% in overweight and obese subjects bespeaks a strong effect, given the relatively short observational period of 12 weeks within the 6-months intervention. A minimum weight loss of 5% has been suggested to be required for clinically relevant hormonal improvements [326], with others arbitrarily setting the

bar somewhat lower at 3% for the definition of successful long-term maintenance of weight loss [327]. The fact that approximately ¾ of the active participants' weight loss originates from a reduction of body fat, bespeaks a clinically desirable effect, as it is the hormonal products of fat tissue which exert the deleterious effects of excess weight on physical health [328, 329].

The correlation of excess body weight with cardiovascular risk for the ELF age cohort has recently been confirmed in the Uppsala Longitudinal Study of Adult Men (ULSAM) [330]. The 1,758 men aged 50 years at study entry in the early 1970s were followed up over 30 years to investigate the correlation between BMI, MetS and cardiovascular morbidity and mortality. Compared to their normal-weight peers without the MetS, overweight and obese men without the MetS had a 1.52 and 1.95 hazard ratio respectively for cardiovascular events.

Taken together, the results of the analyses support the hypotheses of significant changes in anthropometric parameters and body composition from baseline to follow-up and of significant differences between CFL groups. Unexpectedly, a significant change in these parameters was also observed in the CFL- group from baseline to follow-up. However, the magnitude of these changes is of questionable clinical relevance.

Changes In Blood Lipids

The results of the "double-take" on baseline blood lipid measurements in 61 participants, with a period of 7-10 days between measurements, confirmed earlier observations of substantial intra-individual variability of these risk markers [259]. The variability in the ELF sample is somewhat less severe than the one observed by Marcovina et al. These differences in variability have to be viewed in the context of methodological differences between the studies. Marcovina et al. used 4 blood samplings performed at 2-week intervals between samplings. This variability potentially affects the interpretations of intervention effects on lipid parameters and the risk scores derived therefrom. Specifically in clinical practice, where the individual patient's health profile is the benchmark for guiding a personalized intervention, the existence of substantial variability complicates the appraisal of intervention effects.

Considering the results of both investigations, it made intuitive sense to demarcate along an intra-individual threshold of 10% for a change of parameter to be considered clinically relevant from baseline to follow-up. Consequently, participants were dichotomized into successes and failures depending on having or not having improved their baseline lipid values through a 10% reduction (TCH, LDL, TG, TCH/HDL ratio) or increase (HDL) at follow-up.

Of the 5 examined lipid markers (TCH, HDL, LDL, TG, TCH/HDL-ratio) only TCH and TCH/HDL ratio emerged as being significantly improved within- and between-groups.

Changes in HDL were significant in the CFL+ group only when excluding subjects with a baseline HDL value of >= 60 mg/dL. The inter-group changes remained non-significant. However, HDL *per se* has been found to be of little use in the prediction of CVD risk [331],

which makes its clinical utility as a stand-alone marker questionable. Complementary to this view is the earlier observation that TCH/HDL ratio is of superior value in predicting risk [332].

However, given (a) the relatively short duration of the observation period of 6 months, and (b) the acknowledged small effect of changes in PA habits on lipid profiles, known from cross-sectional investigations into the correlation between PA levels and levels of blood lipids [261], the results observed in the ELF sample may nevertheless indicate a positive intervention effect. Whether this effect is reproducible remains questionable, as no effect of PA levels on the cholesterol variables has been observed in another recent investigation into 128 men of comparable mean age (51) as in this study [333].

The small effect observed in the ELF sample, however, is to be examined from a clinical practitioner's viewpoint. The latter's patients are the individuals, not a population as is the case for the public health operator. The clinician's view is probably better served with the odds ratio, which provides for a dichotomization of outcome along clinically meaningful strata of parameter change. Given the 10% threshold for dichotomizing the subjects into strata of presence or absence of meaningful parameter change, the odds ratio of 9 for the TCH/HDL ratio in all subjects with a baseline ratio >4 emerges as the only statistically significant and clinically relevant improvement of lipid profile. Admittedly arbitrary, the 10% threshold emerges naturally from the observation of intra-individual variability, and the ratio cut-off of 4 is supported in published evidence from the Framingham population. In a 20-year follow-up of this population sample of 5251 men and women aged 30-74 years a significant increase of fatal and non-fatal cardiovascular events was observed at each increasing tertile of the TCH/HDL ratio, with a ratio of 4.21, being the cut-off for the lower tertile [334]. Interestingly, the level of the lipids that compose the ratio appeared to have little influence on CVD risk when the ratio itself was favorable. The authors therefore suggested that conservative and less aggressive approaches to optimizing lipid levels are warranted in patients whose TCH/HDL ratio is within the "green" range. The relevance of these observations for the results observed in the ELF sample is obvious: The predictive power of the TCH/HDL ratio for differential diagnosis of risk, given an individual's known levels of lipid fractions, makes the TCH/HDL ratio a suitable biomarker to assess the impact of individual lifestyle changes. The effects of the ELF intervention on this biomarker favor the hypothesis of the underlying strategy being able to positively modify this biomarker.

It will be interesting to see in follow-up investigations whether these effects show more clearly in a ratio which has only very recently emerged as potentially more powerful in risk prediction than the "classic" TCH/HDl ratio: The apoB/apoA ratio of the apo-lipoprotein constituents of the cholesterol fractions, which provide additional information about the size and number of the cholesterol particles, appeared distinctly superior to the TCH/HDL ratio in predicting CVD risk [335].

Nevertheless, the fact remains that even a modest lowering of blood lipids in the range observed here, will have a sizeable public health impact if this lowering happens across large enough groups of the population [336].

Blood Pressure

In this study, blood pressure was measured simply as a component of the PROCAM risk score, not as a hypothesis generating vital sign in its own right.

CRF being the primary outcome parameter, has shown to have no significant relation with blood pressure, with evidence to this extent being reported in population surveys [337], and in clinical trials [338]. Hence, a direct and differential effect of the intervention on blood pressure levels, secondary to the primary outcome of CRF, could not have been formulated *a priori.*

This in itself may be construed as a null-hypothesis, which can be subjected to evaluation with the sample data. The finding of a significant and clinically relevant lowering of diastolic blood pressure, could be construed as a potential rejection of this null hypothesis. This result, however, needs to be assessed in the wider context of this trial.

Hence, the seemingly counterintuitive observation of a significant, and clinically relevant reduction of diastolic pressure by 5 mmHg across CFL groups, with no concomitant reduction in systolic pressure, warranted a closer inspection.

While CRF may not have a direct correlation with blood pressure, the secondary effect – weight loss in response to increased PA - is known to correlate with blood pressure and the hypertensive state.

The Treatment Of Mild Hypertension Study (TOMHS), which randomized its 902 male and female participants (aged 45-69 years) into either lifestyle only or lifestyle combined with 1 of 5 different medications, reported significant changes of blood pressure correlating with weight loss for the lifestyle only participants [339]. Interestingly, the weekly physical activity target, when expressed in calories spent on exercise, was 600 kcal, which makes it very similar to the ELF minimum requirement. The 109 lifestyle-only participants who had lost up to 4.5 kg at the 1-year interim-follow-up had seen a mean reduction of systolic and diastolic pressure of 8.8 and 7.8 mmHg respectively.

These reductions are in excess of what has been reported from meta-analyses by others, which indicate an approximate 1 mmHg reduction for every 1 kg of body weight lost [304, 340].

Stevens et al. reported a mean reduction of 7 and 5 mmHg for systolic and diastolic blood pressure in response to a weight reduction of >4.4 kg after 6 months of a weight loss intervention in 1191 male and female participants [298].

In these contexts, the 4.3 mmHg reduction of systolic blood pressure, experienced by the weight-reducing overweight participants with baseline elevated blood pressure, corresponds with published evidence.

A reduction in CVD, stroke and all-cause mortality of 9%, 14% and 7% respectively had been suggested as the potential effect of a 5mmHg reduction of systolic pressure in the 45-64 year age population [341]. This makes the reduction of blood pressure, witnessed in the Elf sample, of significance to public health. Further investigations with larger sample sizes are warranted to investigate the ELF strategy with respect to blood-pressure specific hypotheses.

PROCAM Score

The PROCAM score, which has been developed from German reference populations [342-344], is widely accepted for risk calculation in this population. The risk factors included in its algorithm are gender, age, HDL, LDL, TG, systolic blood pressure, smoking (yes/no), diabetes (yes/no) and family history of myocardial infarction.

The small absolute changes of this score, observed with within- and between-group significance, need to be viewed relative to the low risk with which the ELF participants had entered the study. While this small absolute reduction of risk may not appear to be of substantial clinical relevance, its statistical significance indicates that the ELF intervention is able to reduce cardiovascular risk, as measured and expressed with the PROCAM score, in its participants. These may be more pronounced at higher risk levels than those presented by the ELF sample.

With respect to the relative changes observed in all three strata, it is worthy to keep in mind that the adherence strata reflect a progressive increase of the duration of self-monitoring (presence of an active controlled feedback loop) from CFL90 to CFL150. It is therefore necessary to keep in mind that the CFL- group of the CFL120 and CFL150 strata contain the data of subjects who met the latency and volume conditions but not the duration condition for the respective strata. These subjects' improved risk scores moderate the effects of unchanged or deteriorating risk scores of the non-adherent subjects in the CFL- groups of the CFL120 & CFL150 strata.

It is tempting to suggest that the progressively moderating gap between the CFL- and CFL+ groups, with a concomitant increase of the risk reduction in the CFL+ groups, is the result of an inverse dose-response relationship between duration of the PA intervention and PROCAM risk score. However, the difference in mean %-risk reduction between the CFL+ groups remained non-significant, which leaves any interpretation speculative only.

It is also informative to compare an individual's actual risk, with achievable minimal risk, given optimal levels of risk factors. For a 50 year old non-diabetic, non-smoking man, with levels of HDL, LDL, TG and systolic pressure of 60 mg/dl, 100 mg/dl, 100 mg/dl and 120 mmHg respectively, the risk of suffering a coronary event within the next 10 years is 1.1% and 1.6%, in the absence respectively presence of a family history of myocardial infarction. Based on this consideration, the change in risk score had been evaluated excluding those participants

whose risk score was below the 1% mark. Given these benchmarks, even the low-risk ELF participants presented a significant potential for further risk reduction.

The proportion of CFL+ participants, who had reduced their PROCAM risk score by at least 10% was nearly 3 times the proportion of CFL- subjects achieving the same reduction (58.9% vs. 20%). This result supports the notion that the ELF intervention effect can be benchmarked with, and expressed in, terms of a risk assessment tool which is commonly used in clinical practice.

The Intervention Effects On The Overweight Participants

The primary target for the ELF behavior change intervention is the sedentary overweight adult. With 51.3% (95% CI 42.0% - 60.5%) of the ELF participants being overweight (25<BMI<30) at baseline, and another 33.9% (95% CI 25.1% - 42.6%) being obese, altogether 85.2% of the ELF sample matched the target profile. The 73.7% of this group who had met the CFL+ criteria in the CFL 90 strata achieved clinically meaningful improvements of CRF and reductions of BMI and of bodyweight, which were approximately 3 times the magnitude of their inactive peers' results. TCH/HDL ratio and PROCAM score improved significantly and to a clinically relevant degree, with non-significant deterioration of the same in the overweight CFL- participants. It is worthy to recall, that this intervention's primary objective was not weight reduction, but improvement of CRF. The expected intervention effect on body weight, as estimated *a priori,* and based on the minimum physical activity target of 3x20' of high intensity interval training per week, was exceeded in this group by a factor of 2. The most important aspect of this observation, however, is not the magnitude of the effect, rather than the reason for its occurrence. The median time spent in exercise (158 minutes weekly) exceeded the minimum requirement by a factor of 2.6.

Contrary to frequently encountered intervention strategies, this trial did neither specify a fixed amount of time to be spent exercising, nor did it set the goal at the 150-minute mark for moderate intensity exercise currently recommended as the weekly minimum to generate health benefits [277]. The intention of this trial's strategy was to define an exercise mode (HIT), which was both short and effective enough to initiate (a) good adherence by being "minimally invasive" with respect to the participants' lifestyles, and thereby (b) stimulate a voluntary gradual expansion of the exercising effort. The adherence rate and self-reported time spent exercising support the validity of this notion.

Of particular interest in this respect is the response obtained from a considerable number of participants, who reported experiencing a marked increase in physical fitness after 3-4 HIT sessions. This improvement manifested either as the ability to perform an increased number of consecutive HIT intervals, or as an increase in power output. In any case, this experience stimulated a subsequently increasing commitment to exercise.

Admittedly qualitative, this observation is in line with published evidence that achieving tangible results relatively quickly after commencing lifestyle change is an important

contributor to success. So has the degree of weight reduction in the first few weeks of a weight loss intervention emerged as a determinant of longer term adherence and weight loss success [345].

Comparison With Peers

One reason for implementing high-intensity interval training as the recommended mode of exercise was the expected time-efficiency of this protocol. As discussed in the introductory section, the protocol of thrice-weekly 20 minutes high-intensity interval training has shown to yield cardiovascular benefits, which are comparable to those achieved with continuous aerobic training of substantially longer duration.

The significantly smaller height and weight and higher body fat content, with concomitant non-significant difference in BMI, reflect the fact that the sample of Miyaki et al. consisted of Japanese subjects. Compared to Europeans, Asians have a higher body fat content at the same BMI value [305, 306]. This may partly explain the significantly lower VO_2peak value observed in this Japanese sample. This, however remains speculative, as, though the data for this sample have been published on a per-subject basis, VO_2peak values were only available as a group mean, which prevented analyses of VO_2peak per kg of lean body mass.

The striking similarity of the intervention effects, with no significant difference other than those, which were expected to be observed for the different ethnic backgrounds, is important for two considerations. Firstly, it indirectly confirms the reliability of the participants' self-reports on exercise volume, which correlates with intervention effect on CRF as measured in VO2peak. Secondly, it bespeaks the efficiency of the ELF intervention, which left the curriculum implementation to the participants without any need or requirement for supervision.

Contrary to clinically supervised PA programs, such as the one of Miyaki et al., ELF participants were instructed to self-monitor, with the objective to engage a controlled feedback loop for the initiation and maintenance of a PA habit in the participant's lifestyle. The results observed and presented in this section support the notion that this strategy yields comparable effects on parameters of cardiovascular health, with adherence rates equal to or better than what has been reported for PA interventions of similar duration.

An Interim Summary

The results of the ELF intervention favor the 4 hypotheses to varying degrees. Adherence to the intervention at follow-up was well within the hypothesized proportion of 75%. Follow-up trials are now warranted to investigate how the applied principles of individualization, monitored self-monitoring and continuity can be applied to preserve this relatively high retention rate and prevent attrition in the longer term.

The intervention effect on cardiorespiratory fitness supports the hypothesis of a significant improvement within- as well as between-groups which is of clinical and public health relevance.

The larger than expected effect on body weight status was secondary to a voluntary 2.5 fold increase of PA over the initially recommended minimum commitment.

Of the lipid profile, only TCH/HDL ratio emerged as a beneficiary with a clinically relevant and significant decrease. Longer-term follow-up trials of the ELF strategy with larger participant numbers are warranted to obtain a more precise estimate of the potential magnitude of this intervention's effect on lipid parameters. That includes the addition of the apolipoprotein ratios as outcome measures, which may be more suitable to determine the intervention effects on blood lipids.

Systolic and diastolic blood pressure showed a somewhat paradoxical response to the intervention with mean diastolic pressure being reduced to a substantially greater degree than systolic pressure. As this parameter was not subject of an *a priori* hypothesis, specific hypothesis testing should be conducted in follow-up investigations.

The overall risk profile, as expressed in the PROCAM score was reduced with within- and between-group significance. The moderate effect, in absolute terms, needs to be viewed in the context of a relatively low mean risk profile in this ELF sample. The trial, however, provides evidence for the utility of the ELF intervention effect to be benchmarked with the widely applied PROCAM score in any given subject population.

Experiences With And Lessons Drawn From The Operationalization Of Intervention Principles

A call has been made very recently for the EU to develop national physical activity recommendations along the new guidelines formulated by the U.S. American Heart Association (AHA) and the American College of Sports Medicine (ACSM) [346]. These guidelines specifically acknowledge the evidence-based need for all healthy adults aged 18-65 to perform either moderate-intensity aerobic exercise for a minimum of 30 min five times weekly, or 20 min of vigorous exercise 3 times weekly or any combination thereof [347].

Individualization

The ELF intervention incorporated this minimum requirement of 3x20 minutes as the basis from which the individualized exercise program was then developed. The latter consisted of (a) CPET-based heart rate controlled exercise recommendation, (b) self-determination of initial exercise targets, which had been (c) agreed upon during a one-to-one initial consultation with the investigator, in which each participant received a detailed assessment of the relevance of PA to his/her individual baseline profile. Individualizing the exercise prescription to each participant's personal cardiopulmonary dynamics maximizes the training

effect. This manifested in tangible and subjectively felt improvements of performance relatively quickly (within the first two weeks after commencing the exercise program), which is a powerful promoter of continued adherence.

Letting participants self-determine their PA volume, given the minimum weekly requirement of 3x20 minutes of high-intensity interval training, yielded a substantially larger actually performed volume of exercise. It is therefore tempting to suggest, that it may not so much be participants' fidelity to a pre-conceived one-size-fits-all exercise curriculum, which lifestyle change program providers should be concerned with. Rather is it getting people to commit to and commence with a physical activity habit, which, if prescribed individually to yield some quick tangible effect, will develop its own momentum. It will be interesting for future research to contrast these two strategies under the *a priori* hypothesis of a significant difference in outcome.

Self-monitoring

Participants were given access to a personal web based file, the electronic lifestyle file (ELF), and were encouraged to self-report the volume of PA performed. The file provides a graphic actual-vs-target feedback on exercise performance. The file also provides for the monitoring of various vital signs, such as body weight, blood pressure and blood sugar either through manual data entry or through telemetric data link with selected measuring equipments. Graphic representations of trends and actual-vs-target performance are presented.

Participants' adherence to the self-monitoring process, expressed as login to the web based personal file, and adherence to the agreed exercise curriculum, were monitored and followed-up through personal contacts, either by phone or by email, in cases of login latency in excess of 7 days, or in cases of potentially under-achieving the 6-weeks cumulative interim targets. While this monitored self-monitoring was referred to by many participants as a strong incentive for staying the intervention course, it generated a substantial work-load which had been underestimated in the trial design. However, from informal group meetings with participants the impression emerged, that it is not so much who "looks over the participant's shoulder" rather than the fact that there is someone, to whom the participant feels accountable to, who does the looking. This suggests that delegating the function of monitoring to participant-selected peers may equally well serve the purpose of encouraging and promoting adherence to behavior change, at least during the critical period of habituating a new behavior. Follow-up trials may therefore contrast modes and combinations of monitoring and feedback, using non-monitored self-monitoring as the control condition.

Self-monitoring however ought to be deployed as recognized promoter of intervention adherence for which there exists substantial and growing published evidence. Reports from the U.S. national weight loss registry, whose registrants present a mean 30 kg weight loss maintained over >5 years, have found self-monitoring, a high level of PA and a low-calorie-low-fat diet as the three most important determinants of weight loss and maintenance of

reduced body weight [123, 205]. In a cross-sectional study, others have found that daily or almost-daily self-monitoring of energy intake and body weight differentiates the successfully weight-reducing individuals from their less successful peers [348].

Self-monitoring based on daily self weighing has been tested as a maintenance strategy in its own right and produced significantly greater success in maintaining weight loss than control [206].

At the time of designing this trial, the focus was on the increase of CRF in a sedentary population. This focus was rooted in the discussed evidence for the substantial health benefits to be derived from enhanced cardiorespiratory function, secondary to sufficiently increased physical activity of moderate-to-high intensity, and independent of BMI. Correspondingly, physical activity was chosen as the primary target for self-monitoring. The intervention's effect on body weight had been substantially underestimated, as much as the voluntary increase of actually performed PA over the intervention's minimum requirement. With a view to the motivating power of quick and tangible achievements for persevering in a behavior change effort, it therefore appears desirable to include daily weighing as the main focus of self-monitoring. A review of the participants' login records has shown that none of the participants had reported body weight on a daily basis. While that does not necessarily translate into a lack of daily weighing, recording of body weight, and the graphic presentation of averaged weight trends, may provide a powerful additional incentive to persevere with the behavior change effort. After all, weight loss is a major objective of most overweight participants in the ELF program.

Body weight is also the central element of the cognitive feedback loop, the two effectors of which are physical activity and dietary intake. The latter is currently being incorporated for self-monitoring into the ELF architecture. With respect to the dose of PA received, a differentiation into its components of intensity, duration and frequency will be provided.

Once completed, the ELF will facilitate self-monitoring of all effectors (PA and dietary intake) as well as all related outcomes (vital signs). Thereby the ELF lends itself to follow-up studies, which investigate its effects in larger and different populations, over longer terms and exploring the hypotheses suggested here.

Continuity

Continuity is a principle of the ELF strategy and emerges from the cycle of diagnostic health profiling, individualized intervention prescription and self-monitoring guided implementation. This trial has seen one revolution of this cycle. Hence, in follow-up studies of longer duration the effectiveness of this cycle over several revolutions will need to be investigated. One essential feature, though, is the unique ability of the ELF to alert investigators to adherence decay in its very early stage. The freely definable alarm functions can be set to identify the latency of login as well as the potential of under- (or over-)achieving individual PA targets. Thereby investigators may concentrate their motivational efforts on those participants who

need them, and avoid wasting such efforts on those who don't. The latter is inevitable in intervention designs of periodic group- or one-on-one interactions between investigators and participants, regardless of the latter's needs or adherence status.

As mentioned in the introductory section, the idea of tele-monitoring individuals had been questioned by some medical practitioners as an Orwellian intrusion into participants lives. The experience with this group of participants refutes this notion. Not only did none of the participants object to having their progress and adherence monitored, many expressly welcomed it as a stimulus to show adherence to the volume of exercise, which they had voluntarily submitted to in the initial consultation. Participants for whom the latency and volume alarms were never raised, occasionally received a personal "keep it up" message, acknowledging their commitment and performance. Coming unexpectedly, these messages turned out to be very well received, with almost all recipients expressing thanks and feelings of strengthened motivation. These messages were not originally planned in the design phase, but incorporated rather *ad hoc* on a sudden insight.

SPECIFIC LESSON DRAWN FROM A WORKSITE INTERVENTION

One advantage of recruiting study participants from within a sufficiently sized industrial complex is the accessibility of subjects to the investigator as well as the accessibility of on-site facilities (laboratory testing, fitness center, corporate medical center) to the subjects. However the concentration of subjects within one such complex has one distinct disadvantage: a high degree of interaction between subjects, either on a professional work-related level or leisure-time related through joint usage of the common fitness facilities. This interconnectedness between intervention participants fosters an inter-subject exchange of personal experiences with the intervention.

In the case of controlled randomized interventions this may affect the outcome of the intervention, specifically when individuals with a high motivation to participate in the intervention arm had been randomized to the control group. These subjects may inevitably learn from their intervention-group peers the details of the intervention curriculum, which the control subjects then consequently may follow on their own and without the knowledge of the investigator. It is easy to see how such a situation potentially attenuates the intervention's effect size. While this did neither affect the outcome nor design of this study, it is a qualitative observation, which was made as an unexpected by-product of having carried out the study, and to which fellow researchers ought to be alerted.

Within the context of the model and theory underlying this intervention, the achieved reduction in bodyweight secondary to a PA intervention is clinically relevant and justifies future investigations, in which the principles of monitored self-monitoring are extended to targets of dietary habits.

STUDY STRENGTHS AND WEAKNESSES

The strengths and weaknesses of this exploratory trial are best discussed in relation to the well-established concepts of validity and reliability.

Validity

Criterion validity refers to a measure's ability to predict a future event. In the larger context of this work, the objective is to reduce the prevalence and incidents of CVD in our population. Clearly, to establish criterion validity for the target behavior (increased physical activity) in achieving this objective is beyond the scope of this trial. On a smaller scale, criterion validity being the degree to which CFL+ subjects maintain their acquired HEPA levels, can only be appraised in extensions of this intervention into longer term follow-up studies. These are planned as a consequence of the results discussed in this paper. Hence, on the score of criterion validity, this work certainly leaves much to desire.

Construct validity is judged by assessing the patterns of correlation between the investigated instrument and outcome variables of known cause-effect associations wit the instrument. VO2peak is the primary measure for this score, and the study results indicate a sufficient validity. This argument extends to the secondary outcomes of body weight and body fat status as well as on the biochemical parameters.

Content validity answers the question whether the measurement tool comprehensively represents all relevant dimensions of the outcome variable. With respect to physical activity, this intervention's measurement is objectionable on the grounds that frequency and duration, having been the subject of participants' self-reports, do not comprehensively measure PA volume when intensity is not measured alongside. This is not the result of neglect but of logistic considerations, which necessitated the weighing of desired measurement detail against technological aspects and those of participant acceptability. In a perfect world, low-cost intensity measurement tools (such as heart rate monitors) report their data directly into a participant's web-based lifestyle file, and participants are well motivated to buy and use these tools appropriately. It is certainly not for lack of effort of the author who has contacted altogether 6 manufacturers of heart rate and other activity monitors with offers to assist in the realization of such tele-monitoring features. However, the response has been negative, which is hoped to change when researchers and others join in availing themselves of the tool developed not only for this research effort, but with the intention to make it available for public health research in general. The subject of acceptability touches on the last but not least aspect of validity…

…*Face validity* which refers to the acceptability of the intervention to the participants. The 76% adherence rate bespeaks a reasonable degree of face validity. So do the responses of the active participants who had been invited into three focus groups with the aim to elicit responses to the questions what worked for them and why and what adjustments need to be made to the ELF as the central tool. Aside from a variety of issues pertaining to the interactive surface of the tool, the uniform response was, that the simple fact of being monitored was the single most important driver of initiating and maintaining the PA curriculum into the previously sedentary lifestyle. I admit culpability of not having performed the focus group sessions in a format that would have allowed their systematic appraisals, a failure which is to be rectified in follow-up investigations.

Reliability

Internal reliability in this context refers to the consistency of self-monitoring (self-reported) physical activity volume. Follow-up investigations need to include an assessment of this matter in sub-groups randomly selected from among intervention participants. The appraisal of test-retest and intersetting reliability is evidently beyond the scope and purpose of theis exploratory trial. Nevertheless these are important aspects to consider when extending this intervention to longer term studies in larger populations.

In addition, it is worth remembering that this study population may not be representative of the population at large. While it does not suffer appreciably from the healthy-participant effect, adherence and outcome may not be replicable to the same extent when this trial's curriculum is translated into populations whose subjects' motivations to participate may differ from this non-randomly selected participant group. However, I contend, that future applications of the tool and the strategies investigated herein will yield similarly encouraging results in participants who have recognized the need for and importance of lifestyle changes to extend health expectancy. I take this optimism from one particular strength of this study, namely its simulation of a real-life application of the intervention within a corporate environment. While participation was subsidized, participants had to contribute from their own financial resources. This reflects what I expect to be the only realistic way of attracting large "multipliers" such as employers and insurers into promoting lifestyle change interventions to the populations under their care. These multipliers operate under the dictum of economic benefit, which extends to investments into health and productivity.

While the economic benefits may be difficult to express in real dollar terms, the benefits accruing to the motivated participant are large and they are known. Non-smoking, normal weight and higher amounts of PA have been identified as contributing the bulk to the reduction of risk for CVD. Evaluations of the Framingham data indicate that high levels of PA, compared to low levels, add 3. 5 years of life expectancy and 3 years of life expectancy free of CVD at age 50 to both men and women [349].

Examining possibly for the first time the combined effects of not-smoking, high physical fitness (as measured by treadmill test) and normal weight status on life expectancy and CVD risk, Lee *et al.* followed 23 657 men aged 30 and older for a mean of 15 years in the Aerobics Center Longitudinal Study (ACLS) [350]. The authors report relative risks of 0.41, 0.23 and 0.31 for CVD events, CVD mortality and all-cause mortality for men meeting all three conditions compared to men who smoked, were inactive, and who had a waist girth $\geq$94 cm. The life expectancy of the latter was also 14 years shorter. According to the authors' estimate only 2-3% of the adult U.S. population meets the three health enhancing criteria, which makes evident the potential economic benefit of interventions which increase this proportion.

I will close this discussion with some insights for the continuation of this line of research as they have emerged from this work and the study results.

In Pursuit Of A Model For The Behavioral Mechanisms That Generate Energy Homeostasis

One can hardly discuss health in general, and the chronic diseases in particular, without engaging the concept of homeostasis.

The medical subject headings (MeSH) of the U.S. National Library of Medicine (NLM) define homeostasis as "The processes whereby the internal environment of an organism tends to remain balanced and stable". While this captures the phenomenon of homeostasis in the sense as initially described, though not in name, by Claude Bernard [351] and further developed by Walter B. Cannon [352], it has two specific implications for the context of this study:

- The biology-behavior dependency
  If homeostasis is the principle of maintaining an organism's internal stability against externally induced perturbations, the organism's behavior is the required mediator between the two. Be it the fight-or-flight response to a stress induced outpouring of catecholamines or the hunting/gathering activities precipitated by the coordinated actions of Leptin and NPY, it is always the appropriate behavioral response, which mediates the resolution of the very perturbations that activated the behavioral drives. The principles of natural selection and adaptation imply that these bio-behavioral feedback loops must have evolved into the variants, which best ensured the organism's survival and reproductive success within its natural habitat.
  This entails the second aspect, namely the behavioral drives' autonomy of operation.
- The autonomy of the behavioral drives
  If survival depends on homeostatic balance and stability, its behavioral mediators ought to have been operating autonomously throughout evolution from the inception of life. As such it should be verifiable as a genetic imprint, manifesting in similarities of behavior across species including humans. The way behavioral research is being conducted supports this notion. By using laboratory animals in experiments, which

> simulate specific external stimuli and internal environments, we not only replicate one species' behavioral phenomena, such as impulsive discounting or ingestive behaviors, in another. We also observe the concordance of these animals' autonomously driven behaviors with their human parallels, which we steadfastly believe to originate from, and therefore also to yield to, our cognitive faculties and free will.

Intuitively it may be difficult to reconcile the dominance of the autonomous behavioral drives with the obvious success of survival and reproduction, conferred upon humans by the uniquely human mental faculties of volition and cognition. In fact, by their mind, humans have bested adaptation to the point where they increase their fitness (in terms of evolution) not by their ability to adapt to a given environment, but by adapting the environment to their abilities. One detrimental consequence, in the context of this study' subject, is the elimination of obligatory physical activity from the self-correcting feedback loops which guard the human organism against homeostatic imbalance. Consequently, initial perturbations potentially develop into chronic imbalances leading to the disease endpoints, which make up the current epidemics of lifestyle disease.

It is here where the human volitional and cognitive faculties need to be engaged to re-establish a salutogenic balance between behavior and physiology. The form of engagement may be best described within the concept of allostasis, introduced by McEwen *et al.* [353].

It is based on the recognition that there is rarely a single and steady homeostatic state. By way of example: If blood glucose is the homeostatic system of interest, changes in its mediators may induce an allostatic state in which blood glucose levels become either elevated or suppressed. A stress-induced increase in catecholamine production is one sample scenario. In it an elevated glucose level is the consequence of an epinephrine-induced down-regulation of the mediator insulin, of insulin sensitivity and up-regulation of hepatic glucose production [354]. At the same time, norepinephrine increases non-insulin mediated glucose uptake into muscle and fat tissue. The resulting allostatic load of elevated blood sugar makes perfect sense in a stress situation, where the need for a fight-or-flight reaction necessitates the release and availability of glucose to fuel the physical reaction. It serves the organism well in the short term, when the release of stress hormones drives the appropriate behavioral fight-or-flight response, ultimately relieving the stress inducing situation. Allostatic load turns into a potentially pathogenic allostatic overload, however, if the behavioral response is inadequate, does not happen or if the triggering environmental situation persists over extended periods of time. The common denominator for these pathogenic scenarios is the disconnect between the physiologic drive and the behavioral response.

Similarly, if an organism, primed for physical activity by the hormonal states, which respond to decreasing energy stores, does not engage in the target behavior, which removes the

hormonal allostatic load, physiologic imbalance is the inevitable result. In this sense allostasis refers to the self-correcting feedback loop in which the physical activity behaviors, with which a human will pay the PA costs imposed by its natural habitat on energy acquisition, re-establish homeostasis as an automatic response to the autonomously operating hormonal excursions, which have cued the human into performing these behaviors.

The sophistication of the human mind has allowed us to (a) remove from our environment the obligatory PA element of this feedback loop, but also to (b) elucidate the mechanisms that drive this loop and the pathogenic consequences of its derailment. While it is tempting to our cognitive faculties to gear into this loop with pharmacological attempts at reestablishing homeostasis, the complexities of neuro-hormonal interaction and the multiplicity of effects of PA on these interactions confound our capability to manipulate them towards the desired results.

These observations suggest not only the need for re-introducing PA and dietary constraints into the modern lifestyle. They also suggest that this reintroduction be modeled along the principles of the self-correcting feedback loop, which has proved to be nature's successful way of maintaining its organisms in homeostatic balance.

Interventions aimed at re-instituting homeostasis need to be framed within the paradigm of the biology-behavior continuum. Essential to these efforts is an appreciation of the fact that specific behavioral inadequacies are inextricably linked to a given individual's physiologic imbalances of which they are causative.

As such, we simply need to insert our cognitive faculties into this self-correcting feedback loop, as the cognitive effector of the PA, which this loop requires to "run the human engine" and to maintain its physical health.

SUGGESTED FOLLOW-UP HYPOTHESES

The strategy, the principles and the tools presented and tested with this study, are one possible approach. The insights emerging from the experience and interaction with the study participants led to the contention that the ELF is an effective facilitator, which engages a self-correcting feedback loop when four essential conditions are met:

1. *Intention*: A cognitive intention to lose weight, as the recognized step to reestablish energy homeostasis.
2. *Engagement*: A daily recording of body weight, physical activity and dietary habits
3. *Feedback*: A daily feedback on body weight trend, averaged in a rolling-window over periods from 1 week to several weeks, each ending at the actual date.
4. *Knowledge, Skills and Abilities*: knowledge about specific exercise and dietary options and the skills and abilities for the practical implementation.

Given the feedback to daily engagement with the ELF, the intent mind will be engaged as the control center of a self-correcting feedback loop. It will drive the individual to consciously and subconsciously search for and select those suitable exercise and dietary strategies, which he finds at his personal disposal.

Based on this insight, the ELF is currently undergoing further development to include dietary monitoring and to facilitate the monitoring of PA volume to a greater precision. The initial experience with several overweight and obese "beta-Testers" strongly suggests the testing of the following hypotheses in randomized controlled trials:

- Daily use of the ELF in a weight reduction intervention leads to significantly larger weight loss in overweight and obese adults,a nd to larger intervention effects on risk parameters, than conventional strategies
- Continued post-intervention utilization of the ELF will facilitate the long-term maintenance of larger weight losses, and the long-term maintenance of larger intervention effects on risk parameters, than discontinuation of ELF utilization.

Taken to their logical conclusion, the considerations and results presented herein advocate the abolition of myopic medical attempts to merely correct risk factors and vital signs to within their normal ranges, in favor of a strategy of reestablishing the salutogenic homeostatic balance as the foundation of health. This is no news to health science. On this subject, Hippocrates is being quoted as having said that "*It is more important to know the person who has a disease, than to know the disease a person has.*"

From the vantage point of today's knowledge about human physiology, coupled with the understanding of its evolutionary origins, Hippocrates' aphorism could be made even more appropriate to today's patient:

It is more important to correct a person's bio-behavioral malfunction that manifests in disease, than to correct the physiological malfunction with which the disease manifests.

REFERENCES

1. Lastra-Gonzalez, G., et al., *Insights into the emerging cardiometabolic prevention and management of diabetes mellitus.* Expert Opin Pharmacother, 2005. **6**(13): p. 2209-21.
2. Li, Y. and P. Agarwal, *A Pathway-Based View of Human Diseases and Disease Relationships.* PLoS ONE, 2009. **4**(2): p. e4346.
3. Govindarajan, G., et al., *The cardiometabolic syndrome as a cardiovascular risk factor.* Am J Med Sci, 2005. **330**(6): p. 311-8.
4. Gewaltig, M.T. and G. Kojda, *Vasoprotection by nitric oxide: mechanisms and therapeutic potential.* Cardiovasc Res, 2002. **55**(2): p. 250-60.
5. Physical Activity Guidelines Advisory Committee, *Physical Activity Guidelines Advisory Committee Report*. 2008, U.S. Department of Health and Human Services: Washington, D.C.
6. Dunn, A.L., *Effectiveness of Lifestyle Physical Activity Interventions to Reduce Cardiovascular Disease.* American Journal of Lifestyle Medicine, 2009: p. 1559827609336067.
7. Cordain, L., et al., *Physical activity, energy expenditure and fitness: an evolutionary perspective.* Int J Sports Med, 1998. **19**(5): p. 328-35.
8. Booth, F.W., et al., *Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy.* J Appl Physiol, 2002. **93**(1): p. 3-30.
9. Booth, F., et al., *Reduced physical activity and risk of chronic disease: the biology behind the consequences.* European Journal of Applied Physiology, 2008. **102**(4): p. 381-390.
10. Neel, J.V., *The "thrifty genotype" in 1998.* Nutr Rev, 1999. **57**(5 Pt 2): p. S2-9.
11. Neel, J.V., *Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"?* Am J Hum Genet, 1962. **14**: p. 353-62.
12. Lederberg, J., *Molecular biology, eugenics and euphenics.* Nature, 1963. **198**: p. 428-9.
13. Troiano, R.P., et al., *Physical activity in the United States measured by accelerometer.* Med Sci Sports Exerc, 2008. **40**(1): p. 181-8.
14. Sjöström, M., et al., *Health-enhancing physical activity across European Union countries: the Eurobarometer study.* Journal of Public Health, 2006. **14**(5): p. 291-300.
15. Weitkunat, R. and M. Moretti, *Health and behavior*, in *ABC of Behavior Change*, J. Kerr, R. Weitkunat, and M. Moretti, Editors. 2005, Elsevier: Edinburgh. p. 17-27.
16. Veerman, J.L., et al., *Stemming the Obesity Epidemic: A Tantalizing Prospect.* Obesity, 2007. **15**(9): p. 2365-2370.
17. Christakis, N.A. and J.H. Fowler, *The Spread of Obesity in a Large Social Network over 32 Years.* N Engl J Med, 2007. **357**(4): p. 370-379.
18. Booth, M.L., et al., *Trends in the Prevalence of Overweight and Obesity among Young Australians, 1985, 1997, and 2004.* Obesity, 2007. **15**(5): p. 1089-1095.
19. Flegal, K.M., et al., *Prevalence and Trends in Obesity Among US Adults, 1999-2000.* JAMA, 2002. **288**(14): p. 1723-1727.
20. Apovian, C.M., *The causes, prevalence and treatment of obesity revisited in 2009: what have we learned so far?* Am J Clin Nutr, 2009: p. ajcn.2009.28473A.
21. Bosy-Westphal, A., et al., *Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure.* Am J Clin Nutr, 2009: p. ajcn.2008.27402.
22. Sodersten, P., et al., *Behavioral neuroendocrinology and treatment of anorexia nervosa.* Front Neuroendocrinol, 2008. **29**(4): p. 445-62.
23. Wannamethee, S.G. and A.G. Shaper, *Physical activity in the prevention of cardiovascular disease: an epidemiological perspective.* Sports Med, 2001. **31**(2): p. 101-14.
24. Sandison, A.T., *Degenerative vascular disease in the Egyptian mummy.* Med Hist, 1962. **6**: p. 77-81.
25. Zimmerman, M.R., *The paleopathology of the cardiovascular system.* Tex Heart Inst J, 1993. **20**(4): p. 252-7.

26. Oeppen, J. and J.W. Vaupel, *Demography. Broken limits to life expectancy.* Science, 2002. **296**(5570): p. 1029-31.
27. Lietava, J., M. Thurzo, and A. Dukat, *Paleodiet and its relation to atherosclerosis.* Ann NY Acad Sci, 1997. **827**(1): p. 382-391.
28. Beaglehole, R., A. Irwin, and T. Prentice, *The World Health Report 2003; Shaping the Future*, in *The World Health Report*. 2003, World Health Organization. p. 204.
29. CDC, *A Public Health Action Plan to Prevent Heart Disease and Stroke*. 2003, U.S. Department of Health and Human Services. p. 132.
30. OECD (2004) *Health Spending in Most OECD Countries Rises, with the U.S. far Outstripping all Others*.
31. OECD, *Health at a Glance: OECD Indicators 2005*. 2005: OECD.
32. *Healthy People 2010: Understanding and Improving Health*. 2000, Washington, DC: U.S. Department of Health and Human Services.
33. Ford, E.S., et al., *Trends in the Prevalence of Low Risk Factor Burden for Cardiovascular Disease Among United States Adults.* Circulation, 2009.
34. Virmani, R., et al., *Pathology of the Vulnerable Plaque.* Journal of the American College of Cardiology, 2006. **47**(8, Supplement 1): p. C13-C18.
35. Lightwood, J., et al., *Forecasting the Future Economic Burden of Current Adolescent Overweight: An Estimate of the Coronary Heart Disease Policy Model.* Am J Public Health, 2009: p. AJPH.2008.152595.
36. Bassuk, S.S. and J.E. Manson, *Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease.* J Appl Physiol, 2005. **99**(3): p. 1193-1204.
37. Powell, K.E., et al., *Physical activity and the incidence of coronary heart disease.* Annu Rev Public Health, 1987. **8**: p. 253-87.
38. Thompson, P.D., et al., *Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity).* Circulation, 2003. **107**(24): p. 3109-16.
39. U.S. Department of Health and Human Services, *Physical Activity and Health: A Report of the Surgeon General.* 1996, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion: Atlanta. p. 300.
40. Hamer, M., E. Stamatakis, and J.M. Saxton, *The impact of physical activity on all-cause mortality in men and women after a cancer diagnosis.* Cancer Causes Control, 2009. **20**(2): p. 225-31.
41. Apullan, F.J., et al., *Usefulness of Self-Reported Leisure-Time Physical Activity to Predict Long-Term Survival in Patients With Coronary Heart Disease.* The American Journal of Cardiology, 2008. **102**(4): p. 375-379.
42. Hakim, A.A., et al., *Effects of walking on coronary heart disease in elderly men: the Honolulu Heart Program.* Circulation, 1999. **100**(1): p. 9-13.
43. Sesso, H.D., R.S. Paffenbarger, Jr., and I.M. Lee, *Physical activity and coronary heart disease in men: The Harvard Alumni Health Study.* Circulation, 2000. **102**(9): p. 975-80.
44. Heitmann, B.L., et al., *Obesity, Leanness, and Mortality: Effect Modification by Physical Activity in Men and Women.* Obesity, 2008. **17**(1): p. 136-142.
45. Orsini, N., et al., *Combined effects of obesity and physical activity in predicting mortality among men.* Journal of Internal Medicine, 2008. **264**(5): p. 442-451.
46. Koster, A., et al., *Joint Associations of Adiposity and Physical Activity With Mortality: The National Institutes of Health-AARP Diet and Health Study.* Am. J. Epidemiol., 2009. **169**(11): p. 1344-1351.
47. Mora, S., et al., *Association of Physical Activity and Body Mass Index With Novel and Traditional Cardiovascular Biomarkers in Women.* JAMA, 2006. **295**(12): p. 1412-1419.
48. von Bonsdorff, M.B., et al., *Physical Activity History and End-of-Life Hospital and Long-Term Care.* J Gerontol A Biol Sci Med Sci, 2009: p. glp029.
49. Stessman, J., et al., *Physical Activity, Function, and Longevity Among the Very Old.* Arch Intern Med, 2009. **169**(16): p. 1476-1483.

50. Mustelin, L., et al., *Physical activity reduces the influence of genetic effects on BMI and waist circumference: a study in young adult twins.* Int J Obes (Lond), 2008.
51. Silventoinen, K., et al., *Modification effects of physical activity and protein intake on heritability of body size and composition.* Am J Clin Nutr, 2009: p. ajcn.2009.27689.
52. Kottke, T.E., et al., *The Comparative Effectiveness of Heart Disease Prevention and Treatment Strategies.* American Journal of Preventive Medicine, 2009. **36**(1): p. 82-88.e5.
53. Mora, S., et al., *Physical Activity and Reduced Risk of Cardiovascular Events. Potential Mediating Mechanisms.* Circulation, 2007: p. CIRCULATIONAHA.107.729939.
54. Lamon, B.D. and D.P. Hajjar, *Inflammation at the Molecular Interface of Atherogenesis: An Anthropological Journey.* Am J Pathol, 2008. **173**(5): p. 1253-1264.
55. Braunwald, E., *Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities.* N Engl J Med, 1997. **337**(19): p. 1360-9.
56. McNeill, A.M., et al., *The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study.* Diabetes Care, 2005. **28**(2): p. 385-90.
57. Wannamethee, S.G., et al., *Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus.* Arch Intern Med, 2005. **165**(22): p. 2644-50.
58. Alberti, G., *Introduction to the metabolic syndrome.* Eur Heart J Suppl, 2005. **7**(suppl_D): p. D3-5.
59. Conen, D., et al., *Metabolic Syndrome, Inflammation, and Risk of Symptomatic Peripheral Artery Disease in Women. A Prospective Study.* Circulation, 2009: p. CIRCULATIONAHA.109.863092.
60. Hansson, G.K., *Inflammation, atherosclerosis, and coronary artery disease.* N Engl J Med, 2005. **352**(16): p. 1685-95.
61. Mach, F., *Inflammation is a crucial feature of atherosclerosis and a potential target to reduce cardiovascular events.* Handb Exp Pharmacol, 2005(170): p. 697-722.
62. Kasapis, C. and P.D. Thompson, *The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review.* J Am Coll Cardiol, 2005. **45**(10): p. 1563-9.
63. Wannamethee, S.G., et al., *Physical activity and hemostatic and inflammatory variables in elderly men.* Circulation, 2002. **105**(15): p. 1785-90.
64. Kadoglou, N.P., et al., *The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus.* Eur J Cardiovasc Prev Rehabil, 2007. **14**(6): p. 837-43.
65. Autenrieth, C., et al., *Association between different domains of physical activity and markers of inflammation.* Med Sci Sports Exerc, 2009. **41**(9): p. 1706-13.
66. Kunsch, C. and R.M. Medford, *Oxidative Stress as a Regulator of Gene Expression in the Vasculature.* Circ Res, 1999. **85**(8): p. 753-766.
67. Ross, R., *Atherosclerosis--an inflammatory disease.* N Engl J Med, 1999. **340**(2): p. 115-26.
68. Clinton, S.K., et al., *Macrophage colony-stimulating factor gene expression in vascular cells and in experimental and human atherosclerosis.* Am J Pathol, 1992. **140**(2): p. 301-16.
69. Virmani, R., et al., *Coronary artery atherosclerosis revisited in Korean war combat casualties.* Arch Pathol Lab Med, 1987. **111**(10): p. 972-6.
70. Tuzcu, E.M., et al., *High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound.* Circulation, 2001. **103**(22): p. 2705-10.
71. Virmani, R., et al., *Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions.* Arterioscler Thromb Vasc Biol, 2000. **20**(5): p. 1262-75.
72. Arbustini, E., et al., *Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction.* Heart, 1999. **82**(3): p. 269-72.
73. Stary, H.C., *The sequence of cell and matrix changes in atherosclerotic lesions of coronary arteries in the first forty years of life.* Eur Heart J, 1990. **11 Suppl E**: p. 3-19.

74. Tedgui, A. and Z. Mallat, *Cytokines in atherosclerosis: pathogenic and regulatory pathways.* Physiol Rev, 2006. **86**(2): p. 515-81.
75. Insull Jr, W., *The Pathology of Atherosclerosis: Plaque Development and Plaque Responses to Medical Treatment.* The American Journal of Medicine, 2009. **122**(1, Supplement 1): p. S3-S14.
76. Busse, R. and I. Fleming, *Endothelial dysfunction in atherosclerosis.* J Vasc Res, 1996. **33**(3): p. 181-94.
77. Furchgott, R.F. and J.V. Zawadzki, *The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine.* Nature, 1980. **288**(5789): p. 373-6.
78. Palmer, R.M., A.G. Ferrige, and S. Moncada, *Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor.* Nature, 1987. **327**(6122): p. 524-6.
79. Ignarro, L.J., et al., *Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide.* Proc Natl Acad Sci U S A, 1987. **84**(24): p. 9265-9.
80. Freedman, J.E., et al., *Deficient platelet-derived nitric oxide and enhanced hemostasis in mice lacking the NOSIII gene.* Circ Res, 1999. **84**(12): p. 1416-21.
81. Lefer, D.J., et al., *Leukocyte-endothelial cell interactions in nitric oxide synthase-deficient mice.* Am J Physiol, 1999. **276**(6 Pt 2): p. H1943-50.
82. Garg, U.C. and A. Hassid, *Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells.* J Clin Invest, 1989. **83**(5): p. 1774-7.
83. Alderton, W.K., C.E. Cooper, and R.G. Knowles, *Nitric oxide synthases: structure, function and inhibition.* Biochem J, 2001. **357**(Pt 3): p. 593-615.
84. Murray, R.K., et al., *Harper's Biochemistry*. 2000: McGraw-Hill.
85. Kuhlencordt, P.J., et al., *Accelerated atherosclerosis, aortic aneurysm formation, and ischemic heart disease in apolipoprotein E/endothelial nitric oxide synthase double-knockout mice.* Circulation, 2001. **104**(4): p. 448-54.
86. Kuhlencordt, P.J., et al., *Genetic deficiency of inducible nitric oxide synthase reduces atherosclerosis and lowers plasma lipid peroxides in apolipoprotein E-knockout mice.* Circulation, 2001. **103**(25): p. 3099-104.
87. Turko, I.V. and F. Murad, *Protein Nitration in Cardiovascular Diseases.* Pharmacol Rev, 2002. **54**(4): p. 619-634.
88. Patel, R.P., et al., *Cell signaling by reactive nitrogen and oxygen species in atherosclerosis.* Free Radic Biol Med, 2000. **28**(12): p. 1780-94.
89. Schopfer, F.J., P.R. Baker, and B.A. Freeman, *NO-dependent protein nitration: a cell signaling event or an oxidative inflammatory response?* Trends Biochem Sci, 2003. **28**(12): p. 646-54.
90. Fridovich, I., *Superoxide anion radical (O2-.), superoxide dismutases, and related matters.* J Biol Chem, 1997. **272**(30): p. 18515-7.
91. Pacher, P., J.S. Beckman, and L. Liaudet, *Nitric oxide and peroxynitrite in health and disease.* Physiol Rev, 2007. **87**(1): p. 315-424.
92. Rubbo, H., et al., *Nitric oxide regulation of superoxide and peroxynitrite-dependent lipid peroxidation. Formation of novel nitrogen-containing oxidized lipid derivatives.* J Biol Chem, 1994. **269**(42): p. 26066-75.
93. Ji, L.L., *Antioxidants and oxidative stress in exercise.* Proc Soc Exp Biol Med, 1999. **222**(3): p. 283-92.
94. Gielen, S., G. Schuler, and R. Hambrecht, *Exercise training in coronary artery disease and coronary vasomotion.* Circulation, 2001. **103**(1): p. E1-6.
95. Joyner, M.J. and D.J. Green, *Excersise protects the cardiovascular system: effects beyond traditional risk factors.* The Journal of Physiology, 2009: p. -.
96. Svindland, A., *The localization of sudanophilic and fibrous plaques in the main left coronary bifurcation.* Atherosclerosis, 1983. **48**(2): p. 139-145.
97. Ku, D.N., et al., *Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress.* Arteriosclerosis, 1985. **5**(3): p. 293-302.
98. Zarins, C.K., et al., *Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress.* Circ Res, 1983. **53**(4): p. 502-14.

99. Nagel, T., et al., *Shear stress selectively upregulates intercellular adhesion molecule-1 expression in cultured human vascular endothelial cells.* J Clin Invest, 1994. **94**(2): p. 885-91.
100. Urbich, C., et al., *Laminar shear stress upregulates integrin expression: role in endothelial cell adhesion and apoptosis.* Circ Res, 2000. **87**(8): p. 683-9.
101. Chien, S., *Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell.* Am J Physiol Heart Circ Physiol, 2007. **292**(3): p. H1209-24.
102. Taylor, C.A., T.J. Hughes, and C.K. Zarins, *Effect of exercise on hemodynamic conditions in the abdominal aorta.* J Vasc Surg, 1999. **29**(6): p. 1077-89.
103. Pepine, C.J., *The impact of nitric oxide in cardiovascular medicine: untapped potential utility.* Am J Med, 2009. **122**(5 Suppl): p. S10-5.
104. Fukai, T., et al., *Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training.* J Clin Invest, 2000. **105**(11): p. 1631-9.
105. Hambrecht, R., et al., *Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial.* Circulation, 2004. **109**(11): p. 1371-8.
106. Miyaki, A., et al., *Effect of habitual aerobic exercise on body weight and arterial function in overweight and obese men.* Am J Cardiol, 2009. **104**(6): p. 823-8.
107. Widlansky, M.E., et al., *The clinical implications of endothelial dysfunction.* J Am Coll Cardiol, 2003. **42**(7): p. 1149-60.
108. Bonetti, P.O., L.O. Lerman, and A. Lerman, *Endothelial dysfunction: a marker of atherosclerotic risk.* Arterioscler Thromb Vasc Biol, 2003. **23**(2): p. 168-75.
109. Walther, C., S. Gielen, and R. Hambrecht, *The effect of exercise training on endothelial function in cardiovascular disease in humans.* Exerc Sport Sci Rev, 2004. **32**(4): p. 129-34.
110. Kojda, G. and R. Hambrecht, *Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy?* Cardiovasc Res, 2005. **67**(2): p. 187-97.
111. Jakicic, J.M., et al., *American College of Sports Medicine position stand. Appropriate intervention strategies for weight loss and prevention of weight regain for adults.* Med Sci Sports Exerc, 2001. **33**(12): p. 2145-56.
112. Talbot, L.A., J.L. Fleg, and E.J. Metter, *Secular trends in leisure-time physical activity in men and women across four decades.* Prev Med, 2003. **37**(1): p. 52-60.
113. Luepker, R.V., et al., *Community education for cardiovascular disease prevention. Morbidity and mortality results from the Minnesota Heart Health Program.* Am J Epidemiol, 1996. **144**(4): p. 351-62.
114. Hoffmeister, H., et al., *Reduction of coronary heart disease risk factors in the German cardiovascular prevention study.* Prev Med, 1996. **25**(2): p. 135-45.
115. Hillsdon, M., et al., *National level promotion of physical activity: results from England's ACTIVE for LIFE campaign.* J Epidemiol Community Health, 2001. **55**(10): p. 755-761.
116. Gidlow, C., et al., *Socio-demographic patterning of referral, uptake and attendance in Physical Activity Referral Schemes.* J Public Health (Oxf), 2007. **29**(2): p. 107-13.
117. Gidlow, C., et al., *Attendance of exercise referral schemes in the UK: A systematic review.* Health Education Journal, 2005. **64**(2): p. 168-186.
118. Robison, J.I. and M.A. Rogers, *Adherence to exercise programmes. Recommendations.* Sports Med, 1994. **17**(1): p. 39-52.
119. O'Neil, H.A. and S.N. Blair, *Enhancing adherence in clinical exercise trials.* Quest, 2001. **53**: p. 310-317.
120. Graffagnino, C.L., et al., *Effect of a community-based weight management program on weight loss and cardiovascular disease risk factors.* Obesity (Silver Spring), 2006. **14**(2): p. 280-8.
121. Miller, W.C., *How effective are traditional dietary and exercise interventions for weight loss?* Med Sci Sports Exerc, 1999. **31**(8): p. 1129-34.
122. Wing, R.R., et al., *Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity.* Diabetes Care, 2001. **24**(1): p. 117-23.
123. Wing, R.R. and J.O. Hill, *SUCCESSFUL WEIGHT LOSS MAINTENANCE.* Annual Review of Nutrition, 2001. **21**(1): p. 323-341.

124. Brandstrom, Y., et al., *Physical activity six months after a myocardial infarction.* Int J Nurs Pract, 2009. **15**(3): p. 191-7.
125. Wanner, M., et al., *Effectiveness of active-online, an individually tailored physical activity intervention, in a real-life setting: randomized controlled trial.* J Med Internet Res, 2009. **11**(3): p. e23.
126. De Cocker, K.A., I.M. De Bourdeaudhuij, and G.M. Cardon, *The effect of a multi-strategy workplace physical activity intervention promoting pedometer use and step count increase.* Health Educ. Res., 2009: p. cyp052.
127. *World Health Organization: Adherence to long-term therapies: evidence for action.* . 2003: Geneva.
128. Stewart, M.A., *Effective physician-patient communication and health outcomes: a review.* CMAJ, 1995. **152**(9): p. 1423-33.
129. Boon, H. and M. Stewart, *Patient-physician communication assessment instruments: 1986 to 1996 in review.* Patient Educ Couns, 1998. **35**(3): p. 161-76.
130. Eden, K.B., et al., *Does counseling by clinicians improve physical activity? A summary of the evidence for the U.S. Preventive Services Task Force.* Ann Intern Med, 2002. **137**(3): p. 208-15.
131. Marcus, B.H., et al., *Efficacy of an individualized, motivationally-tailored physical activity intervention.* Ann Behav Med, 1998. **20**(3): p. 174-80.
132. Winzenberg, T., P. Reid, and K. Shaw, *Assessing physical activity in general practice: a disconnect between clinical practice and public health?* Br J Gen Pract, 2009.
133. WHO, *Integrating prevention into health care*, W.H. Organization, Editor. 2002.
134. Delamater, A.M., *Improving Patient Adherence.* Clinical Diabetes, 2006. **24**(2): p. 71-77.
135. Leventhal, H. and L. Cameron, *Behavioral theories and the problem of compliance.* Patient Education and Counseling, 1987. **10**(2): p. 117-138.
136. Janz, N.K. and M.H. Becker, *The Health Belief Model: a decade later.* Health Educ Q, 1984. **11**(1): p. 1-47.
137. Harrison, J.A., P.D. Mullen, and L.W. Green, *A meta-analysis of studies of the Health Belief Model with adults.* Health Educ Res, 1992. **7**(1): p. 107-16.
138. Taggart, H.M. and S.E. Connor, *The relation of exercise habits to health beliefs and knowledge about osteoporosis.* J Am Coll Health, 1995. **44**(3): p. 127-30.
139. Wallace, L.S., *Osteoporosis prevention in college women: application of the expanded health belief model.* Am J Health Behav, 2002. **26**(3): p. 163-72.
140. Wdowik, M.J., et al., *Expanded health belief model predicts diabetes self-management in college students.* J Nutr Educ, 2001. **33**(1): p. 17-23.
141. Pham, D.T., F. Fortin, and M.F. Thibaudeau, *The role of the Health Belief Model in amputees' self-evaluation of adherence to diabetes self-care behaviors.* Diabetes Educ, 1996. **22**(2): p. 126-32.
142. Mirotznik, J., L. Feldman, and R. Stein, *The health belief model and adherence with a community center-based, supervised coronary heart disease exercise program.* J Community Health, 1995. **20**(3): p. 233-47.
143. Montano, D. and D. Kasprzyk, *The theory of reasoned action and the theory of planned behavior*, in *Health behavior and health education: theory, research, and practice.*, K. Glanz, B. Rimer, and F. Lewis, Editors. 2002, Jossey-Bass publishing: San Francisco.
144. Ajzen, I. and M. Fishbein, *Understanding attitudes and predicting social behavior.* 1980, Englewood Cliffs: Prentice-Hall.
145. Prochaska, J.O., C.C. DiClemente, and J.C. Norcross, *In search of how people change. Applications to addictive behaviors.* Am Psychol, 1992. **47**(9): p. 1102-14.
146. Hutchison, A.J., J.D. Breckon, and L.H. Johnston, *Physical Activity Behavior Change Interventions Based on the Transtheoretical Model: A Systematic Review.* Health Educ Behav, 2008.
147. Callaghan, P., E. Khalil, and I. Morres, *A prospective evaluation of the Transtheoretical Model of Change applied to exercise in young people.* Int J Nurs Stud, 2009.
148. Holden, G., *The relationship of self-efficacy appraisals to subsequent health related outcomes: a meta-analysis.* Soc Work Health Care, 1991. **16**(1): p. 53-93.

149. Martin, M.Y., et al., *Characteristics of insufficiently active hypertensive Black women who volunteer to be in a physical activity promotion intervention: an application of social cognitive theory and the transtheoretical model.* Ethn Dis, 2007. **17**(4): p. 604-10.
150. Rogers, L.Q., et al., *Social cognitive theory and physical activity during breast cancer treatment.* Oncol Nurs Forum, 2005. **32**(4): p. 807-15.
151. Ince, M.L., *Use of a social cognitive theory-based physical-activity intervention on health-promoting behaviors of university students.* Percept Mot Skills, 2008. **107**(3): p. 833-6.
152. Petosa, R.L., R. Suminski, and B. Hortz, *Predicting vigorous physical activity using social cognitive theory.* Am J Health Behav, 2003. **27**(4): p. 301-10.
153. Schwarzer, R., *Modeling Health Behavior Change: How to Predict and Modify the Adoption and Maintenance of Health Behaviors.* Applied Psychology, 2008. **57**(1): p. 1-29.
154. Schwimmer, J.B., T.M. Burwinkle, and J.W. Varni, *Health-Related Quality of Life of Severely Obese Children and Adolescents.* JAMA, 2003. **289**(14): p. 1813-1819.
155. Storch, E.A., et al., *Peer Victimization, Psychosocial Adjustment, and Physical Activity in Overweight and At-Risk-For-Overweight Youth.* J. Pediatr. Psychol., 2007. **32**(1): p. 80-89.
156. CDC. *Overweight and Obesity: Childhood Overweight: Overweight Prevalence*. 2007 20.03.2007]; Available from: http://www.cdc.gov/nccdphp/dnpa/obesity/childhood/prevalence.htm.
157. Latner, J.D. and A.J. Stunkard, *Getting Worse: The Stigmatization of Obese Children.* Obesity Res, 2003. **11**(3): p. 452-456.
158. Staffieri, J.R., *A study of social stereotype of body image in children.* J Pers Soc Psychol, 1967. **7**(1): p. 101-4.
159. Pearce, M.J., J. Boergers, and M.J. Prinstein, *Adolescent Obesity, Overt and Relational Peer Victimization, and Romantic Relationships.* Obesity Res, 2002. **10**(5): p. 386-393.
160. Pierce, J.W. and J. Wardle, *Cause and effect beliefs and self-esteem of overweight children.* J Child Psychol Psychiatry, 1997. **38**(6): p. 645-50.
161. Schur, E.A., M. Sanders, and H. Steiner, *Body dissatisfaction and dieting in young children.* Int J Eat Disord, 2000. **27**(1): p. 74-82.
162. Ritchie, L., et al., *Pediatric Overweight: A Rreview of the Literature*. 2001, University of California, Berkeley. p. 130.
163. Carr, D. and M.A. Friedman, *Is obesity stigmatizing? Body weight, perceived discrimination, and psychological well-being in the United States.* J Health Soc Behav, 2005. **46**(3): p. 244-59.
164. Puhl, R. and K.D. Brownell, *Bias, Discrimination, and Obesity.* Obesity Res, 2001. **9**(12): p. 788-805.
165. Brown, I., *Nurses' attitudes towards adult patients who are obese: literature review.* Journal of Advanced Nursing, 2006. **53**(2): p. 221-232.
166. Charles L. Baum Ii, W.F.F., *The wage effects of obesity: a longitudinal study.* Health Economics, 2004. **13**(9): p. 885-899.
167. Chen, E.Y. and M. Brown, *Obesity Stigma in Sexual Relationships.* Obesity Res, 2005. **13**(8): p. 1393-1397.
168. Chambliss, H.O., C.E. Finley, and S.N. Blair, *Attitudes toward obese individuals among exercise science students.* Med Sci Sports Exerc, 2004. **36**(3): p. 468-74.
169. Geier, A.B., M.B. Schwartz, and K.D. Brownell, *"Before and after" diet advertisements escalate weight stigma.* Eat Weight Disord, 2003. **8**(4): p. 282-8.
170. Wang, S.S., K.D. Brownell, and T.A. Wadden, *The influence of the stigma of obesity on overweight individuals.* Int J Obes Relat Metab Disord, 2004. **28**(10): p. 1333-7.
171. Kirby, K.N., *Bidding on the Future: Evidence Against Normative Discounting of Delayed Rewards.* Journal of Experimental Psychology: General, 1997. **126**(1): p. 54-70.
172. Green, L. and J. Myerson, *A Discounting Framework for Choice With Delayed and Probabilistic Rewards.* Psychological Bulletin, 2004. **130**(5): p. 769-792.
173. Ainslie, G., *Breakdown of Will*. 1 ed. 2001, Cambridge: Cambridge University Press. 270.

174. Kirby, K.N. and B. Guastello, *Making Choices in Anticipation of Similar Future Choices Can Increase Self-Control.* Journal of Experimental Psychology: Applied, 2001. **7**(2): p. 154-164.
175. Ainslie, G. and J.R. Monterosso, *Building blocks of self-control: increased tolerance for delay with bundled rewards.* J Exp Anal Behav, 2003. **79**(1): p. 37-48.
176. Wade, T.R., H. de Wit, and J.B. Richards, *Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats.* Psychopharmacology (Berl), 2000. **150**(1): p. 90-101.
177. Green, L., et al., *Discounting of delayed food rewards in pigeons and rats: is there a magnitude effect?* J Exp Anal Behav, 2004. **81**(1): p. 39-50.
178. Green, L., et al., *Temporal discounting in choice between delayed rewards: the role of age and income.* Psychol Aging, 1996. **11**(1): p. 79-84.
179. Robinson, T.E. and K.C. Berridge, *The neural basis of drug craving: an incentive-sensitization theory of addiction.* Brain Res Brain Res Rev, 1993. **18**(3): p. 247-91.
180. Berridge, K.C., *Food reward: brain substrates of wanting and liking.* Neurosci Biobehav Rev, 1996. **20**(1): p. 1-25.
181. Levine, A.S., C.M. Kotz, and B.A. Gosnell, *Sugars and Fats: The Neurobiology of Preference.* J. Nutr., 2003. **133**(3): p. 831S-834.
182. Beauchamp, G.K. and B.J. Cowart, *Congenital and experiential factors in the development of human flavor preferences.* Appetite, 1985. **6**(4): p. 357-72.
183. Ueno, A., Y. Ueno, and M. Tomonaga, *Facial responses to four basic tastes in newborn rhesus macaques (Macaca mulatta) and chimpanzees (Pan troglodytes).* Behav Brain Res, 2004. **154**(1): p. 261-71.
184. Carlsen, M., et al., *The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide.* Nutrition Journal, 2010. **9**(1): p. 3.
185. Pecina, S., et al., *Hyperdopaminergic Mutant Mice Have Higher "Wanting" But Not "Liking" for Sweet Rewards.* J. Neurosci., 2003. **23**(28): p. 9395-9402.
186. Avena, N.M., et al., *Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response.* Neuroscience, 2006. **139**(3): p. 813-20.
187. Cannon, C.M. and M.R. Bseikri, *Is dopamine required for natural reward?* Physiol Behav, 2004. **81**(5): p. 741-8.
188. Pecina, S., J. Schulkin, and K.C. Berridge, *Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress?* BMC Biol, 2006. **4**: p. 8.
189. Dallman, M.F., et al., *Chronic stress and obesity: A new view of "comfort food".* PNAS, 2003. **100**(20): p. 11696-11701.
190. Seymour, B., *Carry on Eating: Neural Pathways Mediating Conditioned Potentiation of Feeding.* J. Neurosci., 2006. **26**(4): p. 1061-1062.
191. Kiefer, F. and M. Grosshans, *[What can addiction research contribute towards the understanding of obesity?].* Nervenarzt, 2009.
192. Finer, N., *Sibutramine: its mode of action and efficacy.* Int J Obes Relat Metab Disord, 2002. **26 Suppl 4**: p. S29-33.
193. Craig, W., *Appetites and Aversions as Constituents of Instincts.* Proc Natl Acad Sci U S A, 1917. **3**(12): p. 685-8.
194. Tatemoto, K., *Neuropeptide Y: complete amino acid sequence of the brain peptide.* Proc Natl Acad Sci U S A, 1982. **79**(18): p. 5485-9.
195. Kalra, S.P., et al., *Interacting Appetite-Regulating Pathways in the Hypothalamic Regulation of Body Weight.* Endocr Rev, 1999. **20**(1): p. 68-100.
196. Ammar, A.A., et al., *NPY-leptin: opposing effects on appetitive and consummatory ingestive behavior and sexual behavior.* Am J Physiol Regul Integr Comp Physiol, 2000. **278**(6): p. R1627-33.
197. Harris, R.B., *Role of set-point theory in regulation of body weight.* FASEB J, 1990. **4**(15): p. 3310-8.
198. Berthoud, H.R., *Multiple neural systems controlling food intake and body weight.* Neurosci Biobehav Rev, 2002. **26**(4): p. 393-428.
199. Larhammar, D. and E. Salaneck, *Molecular evolution of NPY receptor subtypes.* Neuropeptides, 2004. **38**(4): p. 141-51.

200. Cerda-Reverter, J.M., et al., *Molecular evolution of the neuropeptide Y (NPY) family of peptides: cloning of three NPY-related peptides from the sea bass (Dicentrarchus labrax).* Regul Pept, 2000. **95**(1-3): p. 25-34.
201. Nergardh, R., et al., *Neuropeptide Y facilitates activity-based-anorexia.* Psychoneuroendocrinology, 2007. **32**(5): p. 493-502.
202. Spatz, C. and S.D. Jones, *Starvation anorexia as an explanation of "self-starvation" of rats living in activity wheels.* J Comp Physiol Psychol, 1971. **77**(2): p. 313-7.
203. Naslund, E., et al., *Associations of leptin, insulin resistance and thyroid function with long-term weight loss in dieting obese men.* J Intern Med, 2000. **248**(4): p. 299-308.
204. Eek, J.F. and P.-O. Ostergren, *Factors associated with BMI change over five years in a Swedish adult population. Results from the Scania Public Health Cohort Study.* Scand J Public Health, 2009: p. 1403494809104359.
205. Wing, R.R. and S. Phelan, *Long-term weight loss maintenance.* Am J Clin Nutr, 2005. **82**(1): p. 222S-225.
206. Wing, R.R., et al., *A Self-Regulation Program for Maintenance of Weight Loss.* N Engl J Med, 2006. **355**(15): p. 1563-1571.
207. Stubbe, J.H., et al., *Genetic influences on exercise participation in 37,051 twin pairs from seven countries.* PLoS ONE, 2006. **1**: p. e22.
208. Stefan, N., et al., *The Gln223Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism.* Int J Obes Relat Metab Disord, 2002. **26**(12): p. 1629-32.
209. DE MOOR, M.H.M., et al., *Genome-Wide Association Study of Exercise Behavior in Dutch and American Adults.* Medicine & Science in Sports & Exercise, 2009. **41**(10): p. 1887-1895.
210. Johnson, F.R., et al., *High-Risk Individuals' Willingness to Pay for Diabetes Risk-Reduction Programs.* Diabetes Care, 2006. **29**(6): p. 1351-1356.
211. Venditti, E.M., et al., *First versus repeat treatment with a lifestyle intervention program: attendance and weight loss outcomes.* Int J Obes (Lond), 2008.
212. King, N.A., et al., *Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss.* Int J Obes (Lond), 2007.
213. Dionne, F.T., et al., *Mitochondrial DNA sequence polymorphism, VO2max, and response to endurance training.* Med Sci Sports Exerc, 1993. **25**(7): p. 766-74.
214. Bouchard, C. and T. Rankinen, *Individual differences in response to regular physical activity.* Med Sci Sports Exerc, 2001. **33**(6 Suppl): p. S446-51; discussion S452-3.
215. Koenig, W., et al., *C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany.* Circulation, 2004. **109**(11): p. 1349-53.
216. Kraushaar, L. and A. Kramer, *Are we losing the battle against cardiometabolic disease? The case for a paradigm shift in primary prevention.* BMC Public Health, 2009. **9**(1): p. 64.
217. Stevens, V., *Learning habits and skills*, in *The ABC of Behavior Change*, J. Kerr, R. Weitkunat, and M. Moretti, Editors. 2005, Elsevier: Edinburgh.
218. Izawa, K.P., et al., *Effect of the self-monitoring approach on exercise maintenance during cardiac rehabilitation: a randomized, controlled trial.* Am J Phys Med Rehabil, 2005. **84**(5): p. 313-21.
219. Gregory, S., Y. Bostock, and K. Backett-Milburn, *Recovering from a heart attack: a qualitative study into lay experiences and the struggle to make lifestyle changes.* Fam Pract, 2006. **23**(2): p. 220-5.
220. Shepich, J., J.M. Slowiak, and A. Keniston, *Do subsidization and monitoring enhance adherence to prescribed exercise?* Am J Health Promot, 2007. **22**(1): p. 2-5.
221. Burke, L.E., et al., *SMART trial: A randomized clinical trial of self-monitoring in behavioral weight management-design and baseline findings.* Contemp Clin Trials, 2009.
222. Maric, B., et al., *A systematic review of telemonitoring technologies in heart failure.* Eur J Heart Fail, 2009. **11**(5): p. 506-17.
223. Sehnert, W. and T. Mengden, *Möglichkeiten der Telemedizin bei Hochdruckpatienten.* Medizinische Klinik, 2009. **104**(4): p. 314–22.
224. Bateson, M., D. Nettle, and G. Roberts, *Cues of being watched enhance cooperation in a real-world setting.* Biol Lett, 2006. **2**(3): p. 412-4.

225. Haselton, M.G. and D.M. Buss, *Error management theory: A new perspective on biases in cross-sex mind reading.* Journal of Personality and Social Psychology, 2000. **78**(1): p. 81-91.
226. Nowak, M.A. and K. Sigmund, *Evolution of indirect reciprocity.* Nature, 2005. **437**(7063): p. 1291-1298.
227. Kraushaar, L. and A. Krämer, *Individualized primary prevention of chronic cardio-metabolic disease - a paradigm change long overdue*, in *Evidenzbasierte Primärversorgung und Pflege; 9. Jahrestagung Deutsches Netzwerk Evidenzbasierte Medizin und Kongress der Deutschen Gesellschaft für Pflegewissenschaft*. 2008: Witten.
228. O'Donovan, G., et al., *Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate- or high-intensity exercise of equal energy cost.* J Appl Physiol, 2005. **98**(5): p. 1619-1625.
229. Dishman, R., *The Problem of Exercise Adherence: Fighting Sloth in Nations With Market Economies.* Quest, 2001. **53**(3): p. 279-294.
230. Christen, A., et al., *Rate of change and instability in body mass index, insulin resistance and lipid metabolism as predictors of atherosclerotic vascular disease.* J Clin Endocrinol Metab, 2007: p. jc.2006-2267.
231. Hernan, W.H., et al., *Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program.* Diabetes Care, 2003. **26**(1): p. 36-47.
232. Eddy, D.M., L. Schlessinger, and R. Kahn, *Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes.* Ann Intern Med, 2005. **143**(4): p. 251-64.
233. Hanna Tolonen, Kari Kuulasmaa, and E. Ruokokoski. *MONICA Population Survey Data Book*. 2000; Available from: http://www.ktl.fi/publications/monica/surveydb/title.htm.
234. *Mikrozensus - Fragen zur Gesundheit. Körpermaße der Bevölkerung*. 2006, Statistisches Bundesamt: Wiesbaden.
235. Atlantis, E., et al., *Worksite intervention effects on physical health: a randomized controlled trial.* Health Promot Int, 2006. **21**(3): p. 191-200.
236. Laukkanen, J.A., et al., *The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study.* Eur Heart J, 2004. **25**(16): p. 1428-37.
237. Ainsworth, B.E., et al., *Compendium of physical activities: an update of activity codes and MET intensities.* Med Sci Sports Exerc, 2000. **32**(9 Suppl): p. S498-504.
238. Balady, G.J., et al., *ACSM's Guidelines for Exercise Testing and Prescription*. 6 ed, ed. B. Franklin. 2000, Philadelphia: Lippincott Williams & Wilins.
239. Miller, E.R., 3rd, et al., *Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT).* Hypertension, 2002. **40**(5): p. 612-618.
240. Kraus, W.E., et al., *Effects of the amount and intensity of exercise on plasma lipoproteins.* N Engl J Med, 2002. **347**(19): p. 1483-92.
241. Leon, A.S. and O.A. Sanchez, *Response of blood lipids to exercise training alone or combined with dietary intervention.* Med Sci Sports Exerc, 2001. **33**(6 Suppl): p. S502-15; discussion S528-9.
242. Thompson, P.D., et al., *The acute versus the chronic response to exercise.* Med Sci Sports Exerc, 2001. **33**(6 Suppl): p. S438-45; discussion S452-3.
243. Ades, P.A., et al., *High-Calorie-Expenditure Exercise. A New Approach to Cardiac Rehabilitation for Overweight Coronary Patients.* Circulation, 2009: p. CIRCULATIONAHA.108.834184.
244. King, A.C., et al., *Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women aged 50 to 65 years.* Circulation, 1995. **91**(10): p. 2596-604.
245. Frison, L. and S.J. Pocock, *Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design.* Stat Med, 1992. **11**(13): p. 1685-704.
246. Washburn, R.A., et al., *The validity of the Stanford Seven-Day Physical Activity Recall in young adults.* Med Sci Sports Exerc, 2003. **35**(8): p. 1374-80.
247. Marc Bonnefoy, et al., *Simultaneous Validation of Ten Physical Activity Questionnaires in Older Men: A Doubly Labeled Water Study.* Journal of the American Geriatrics Society, 2001. **49**(1): p. 28-35.

248. Westerterp, K.R., *Assessment of physical activity: a critical appraisal.* Eur J Appl Physiol, 2009.
249. Wareham, N.J., et al., *Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.* Public Health Nutr, 2003. **6**(4): p. 407-13.
250. Seale, J., C. Miles, and C.E. Bodwell, *Sensitivity of methods for calculating energy expenditure by use of doubly labeled water.* J Appl Physiol, 1989. **66**(2): p. 644-52.
251. Conway, J.M., et al., *Comparison of energy expenditure estimates from doubly labeled water, a physical activity questionnaire, and physical activity records.* Am J Clin Nutr, 2002. **75**(3): p. 519-525.
252. Bosy-Westphal, A., et al., *Phase Angle From Bioelectrical Impedance Analysis: Population Reference Values by Age, Sex, and Body Mass Index.* JPEN J Parenter Enteral Nutr, 2006. **30**(4): p. 309-316.
253. Bosy-Westphal, A., et al., *Patterns of bioelectrical impedance vector distribution by body mass index and age: implications for body-composition analysis.* Am J Clin Nutr, 2005. **82**(1): p. 60-68.
254. van Dokkum, W., J. Schrijver, and J.A. Wesstra, *Variability in man of the levels of some indices of nutritional status over a 60-d period on a constant diet.* Eur J Clin Nutr, 1990. **44**(9): p. 665-74.
255. Nazir, D.J., et al., *Monthly intra-individual variation in lipids over a 1-year period in 22 normal subjects.* Clinical Biochemistry, 1999. **32**(5): p. 381-389.
256. Aguzzi, F., N. Poggi, and M. Maggi, *Some data on intra-individual variability in high-density-lipoprotein cholesterol.* Clin Chem, 1979. **25**(9): p. 1671.
257. Holzel, W.G., *Intra-individual variation of some analytes in serum of patients with insulin-dependent diabetes mellitus.* Clin Chem, 1987. **33**(1): p. 57-61.
258. Garnotel, R., et al., *Long-term variability of serum lipoprotein(a) concentrations in healthy fertile women.* Clin Chem Lab Med, 1998. **36**(5): p. 317-21.
259. Marcovina, S.M., V.P. Gaur, and J.J. Albers, *Biological variability of cholesterol, triglyceride, low- and high-density lipoprotein cholesterol, lipoprotein(a), and apolipoproteins A-I and B.* Clin Chem, 1994. **40**(4): p. 574-8.
260. Smith, S.J., et al., *Biological variability in concentrations of serum lipids: sources of variation among results from published studies and composite predicted values.* Clin Chem, 1993. **39**(6): p. 1012-22.
261. Fan, A., et al., *Validation of reported physical activity for cholesterol control using two different physical activity instruments.* Vasc Health Risk Manag, 2009. **5**: p. 649-61.
262. McConnell, T., *Cardiorespiratory Assessment of Apparently Healthy Populations*, in *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription*. 2001, LWW: Philadelphia. p. 361-365.
263. Rolf F. Kroidl, S. Schwarz, and B. Lehnigk, *Technische und formale Grundlagen*, in *Kursbuch Spiroergometrie*. 2007, Thieme: Stuttgart. p. 16.
264. Meyer, T., et al., *Reliability of gas exchange measurements from two different spiroergometry systems.* Int J Sports Med, 2001. **22**(8): p. 593-7.
265. Wasserman, K., et al., *Principles of Exercise Testing and Interpretation*. 4 ed. 2005, Philadelphia: Lippincott Williams & Wilkins.
266. Altman, D.G., *Practical Statistics For Medical Research*. 1991, Boca Raton, Florida: Chapman & Hall/CRC.
267. Rosner, B., *Fundamentals of Biostatistics*. 6th Edition ed. 2006, Belmont, CA: Thomson Brooks/Cole.
268. Cohen, J., *Statistical power analysis for the behavioral sciences*. 2nd ed. 1988, New York :: Academic Press.
269. Bland, M., *Significance Tests*, in *An Introduction to Medical Statistics*. 2000, Oxford University Press: Oxford. p. 137-155.
270. Perneger, T.V., *What's wrong with Bonferroni adjustments.* BMJ, 1998. **316**(7139): p. 1236-8.
271. Levene, H., *Robust tests for equality of variances*, in *Contributions to Probability and Statistics*, I. Olkin, Editor. 1960, Stanford University Press: Palo Alto, California. p. 278–292.
272. Brown, M.B. and A.B. Forsythe, *Robust Tests for the Equality of Variances.* Journal of the American Statistical Association, 1974. **69**(346): p. 364-367.

273. Courneya, K.S., et al., *A longitudinal study of exercise barriers in colorectal cancer survivors participating in a randomized controlled trial.* Ann Behav Med, 2005. **29**(2): p. 147-53.
274. Ziebland, S., et al., *Lack of willpower or lack of wherewithal? "Internal" and "external" barriers to changing diet and exercise in a three year follow-up of participants in a health check.* Soc Sci Med, 1998. **46**(4-5): p. 461-5.
275. El Ansari, W. and G. Lovell, *Barriers to exercise in younger and older non-exercising adult women: a cross sectional study in London, United Kingdom.* Int J Environ Res Public Health, 2009. **6**(4): p. 1443-55.
276. Mudd, L.M., et al., *Physical activity recommendations: an alternative approach using energy expenditure.* Med Sci Sports Exerc, 2008. **40**(10): p. 1757-63.
277. Donnelly, J.E., et al., *American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults.* Med Sci Sports Exerc, 2009. **41**(2): p. 459-71.
278. Brooks, G.A., et al., *Chronicle of the Institute of Medicine physical activity recommendation: how a physical activity recommendation came to be among dietary recommendations.* Am J Clin Nutr, 2004. **79**(5): p. 921S-930.
279. Leitzmann, M.F., et al., *Physical activity recommendations and decreased risk of mortality.* Arch Intern Med, 2007. **167**(22): p. 2453-60.
280. Hamer, M. and E. Stamatakis, *Physical activity and risk of cardiovascular disease events: inflammatory and metabolic mechanisms.* Med Sci Sports Exerc, 2009. **41**(6): p. 1206-11.
281. Babraj J, et al., *Extremely short duration high intensity training substantially improves insulin action in young sedentary males* BMC Endocrine Disorders, 2009. **9**(3).
282. Fairchild, T.J., et al., *Glycogen synthesis in muscle fibers during active recovery from intense exercise.* Med Sci Sports Exerc, 2003. **35**(4): p. 595-602.
283. Tjonna, A.E., et al., *Aerobic Interval Training Versus Continuous Moderate Exercise as a Treatment for the Metabolic Syndrome. A Pilot Study.* Circulation, 2008: p. CIRCULATIONAHA.108.772822.
284. Wisloff, U., et al., *Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study.* Circulation, 2007. **115**(24): p. 3086-94.
285. Nilsson, B.B., et al., *Group-based aerobic interval training in patients with chronic heart failure: Norwegian Ullevaal Model.* Phys Ther, 2008. **88**(4): p. 523-35.
286. Markovitch, D., R.M. Tyrrell, and D. Thompson, *Acute moderate-intensity exercise in middle-aged men has neither an anti- nor proinflammatory effect.* J Appl Physiol, 2008. **105**(1): p. 260-265.
287. Tyldum, G.A., et al., *Endothelial Dysfunction Induced by Post-Prandial Lipemia: Complete Protection Afforded by High-Intensity Aerobic Interval Exercise.* Journal of the American College of Cardiology, 2009. **53**(2): p. 200-206.
288. US Department of Health and Human Services, *Objectives 22-2 and 22-3. In: Healthy people 2010 (conference ed, in 2 vols)*, US Department of Health and Human Services: Washington, DC.
289. Solomon, T.P.J., et al., *Effects of exercise training and diet on lipid kinetics during free fatty acid-induced insulin resistance in older obese humans with impaired glucose tolerance.* Am J Physiol Endocrinol Metab, 2009. **297**(2): p. E552-559.
290. Robertson, R.J., *Perceived Exertion for Practitioners. Rating Effort With the OMNI Picture System*. 2004, Champaign, Ill.: Human Kinetics.
291. Utter, A.C., et al., *Validation of the Adult OMNI Scale of perceived exertion for walking/running exercise.* Med Sci Sports Exerc, 2004. **36**(10): p. 1776-80.
292. Robertson, R.J., et al., *Concurrent validation of the OMNI perceived exertion scale for resistance exercise.* Med Sci Sports Exerc, 2003. **35**(2): p. 333-41.
293. Bundesamt, S., *Mikrozensus - Fragen zur Gesundheit, Körpermasse der Bevölkerung*, S. Bundesamt, Editor. 2006: Wiesbaden.
294. Anshel, M.H. and M. Kang, *An outcome-based action study on changes in fitness, blood lipids, and exercise adherence, using the disconnected values (intervention) model.* Behav Med, 2007. **33**(3): p. 85-100.
295. Flegal, K.E., et al., *Adherence to yoga and exercise interventions in a 6-month clinical trial.* BMC Complement Altern Med, 2007. **7**: p. 37.

296. Colley, R.C., et al., *Variability in adherence to an unsupervised exercise prescription in obese women.* Int J Obes (Lond), 2008. **32**(5): p. 837-44.
297. Cooper, C.B. and T.W. Storer, *Exercise testing and interpretation. A practical approach.* 2001, Cambridge: Cambridge University Press.
298. Stevens, V.J., et al., *Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II.* Ann Intern Med, 2001. **134**(1): p. 1-11.
299. Moore, L.L., et al., *Weight loss in overweight adults and the long-term risk of hypertension: the Framingham study.* Arch Intern Med, 2005. **165**(11): p. 1298-303.
300. Wood, P.D., et al., *Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise.* N Engl J Med, 1988. **319**(18): p. 1173-9.
301. Ross, R., et al., *Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial.* Ann Intern Med, 2000. **133**(2): p. 92-103.
302. Bland, M., *The Analysis of Cross-Tabulations*, in *An Introduction to Medical Statistics*. 2000, Oxford University Press: Oxford. p. 230-256.
303. Carretero, O.A. and S. Oparil, *Essential Hypertension : Part I: Definition and Etiology.* Circulation, 2000. **101**(3): p. 329-335.
304. Neter, J.E., et al., *Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials.* Hypertension, 2003. **42**(5): p. 878-84.
305. Wang, J., et al., *Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements.* Am J Clin Nutr, 1994. **60**(1): p. 23-8.
306. Kagawa, M., et al., *Differences in the relationship between BMI and percentage body fat between Japanese and Australian-Caucasian young men.* Br J Nutr, 2006. **95**(5): p. 1002-7.
307. Lee, K.L., et al., *Clinical judgment and statistics. Lessons from a simulated randomized trial in coronary artery disease.* Circulation, 1980. **61**(3): p. 508-15.
308. Bland, M., *Comparing the Means of Small Samples*, in *An Introduction To Medical Statistics*. 2000, Oxford University Press: Oxford. p. 156-184.
309. Kriska, A.M., et al., *A randomized exercise trial in older women: increased activity over two years and the factors associated with compliance.* Med Sci Sports Exerc, 1986. **18**(5): p. 557-62.
310. King, A.C., et al., *Can we identify who will adhere to long-term physical activity? Signal detection methodology as a potential aid to clinical decision making.* Health Psychol, 1997. **16**(4): p. 380-9.
311. Carter, W.B., et al., *Participation of older adults in health programs and research: a critical review of the literature.* Gerontologist, 1991. **31**(5): p. 584-92.
312. Lissner, L., B.L. Heitmann, and C. Bengtsson, *Population studies of diet and obesity.* Br J Nutr, 2000. **83 Suppl 1**: p. S21-4.
313. Remington, R.D., H.L. Taylor, and E.R. Buskirk, *A method for assessing volunteer bias and its application to a cardiovascular disease prevention progamme involving physical activity.* J Epidemiol Community Health, 1978. **32**(4): p. 250-5.
314. McMichael, A.J., R. Spirtas, and L.L. Kupper, *An epidemiologic study of mortality within a cohort of rubber workers, 1964-72.* J Occup Med, 1974. **16**(7): p. 458-64.
315. Li, C.-Y. and F.-C. Sung, *A review of the healthy worker effect in occupational epidemiology.* Occup Med (Lond), 1999. **49**(4): p. 225-229.
316. Myers, J., et al., *Exercise capacity and mortality among men referred for exercise testing.* N Engl J Med, 2002. **346**(11): p. 793-801.
317. Michie, S., et al., *Effective techniques in healthy eating and physical activity interventions: a meta-regression.* Health Psychol, 2009. **28**(6): p. 690-701.
318. Welsh, E., et al., *Is frequent self-weighing associated with poorer body satisfaction? Findings from a phone-based weight loss trial.* J Nutr Educ Behav, 2009. **41**(6): p. 425-8.
319. Roger, V.L., et al., *Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota.* Circulation, 1998. **98**(25): p. 2836-41.
320. Amati, F., et al., *Separate and combined effects of exercise training and weight loss on exercise efficiency and substrate oxidation.* J Appl Physiol, 2008: p. 90384.2008.

321. Field, A.E., et al., *Weight-control behaviors and subsequent weight change among adolescents and young adult females.* Am J Clin Nutr, 2010. **91**(1): p. 147-153.
322. Goldsmith, R., et al., *Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects.* Am J Physiol Regul Integr Comp Physiol, 2010. **298**(1): p. R79-88.
323. Manini, T.M., *Energy expenditure and aging.* Ageing Research Reviews, 2010. **9**(1): p. 1-11.
324. Weinert, D., *Circadian temperature variation and ageing.* Ageing Research Reviews, 2010. **9**(1): p. 51-60.
325. Hu, G., et al., *Joint Effects of Physical Activity, Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio on the Risk of Heart Failure.* Circulation, 2010: p. CIRCULATIONAHA.109.887893.
326. Varady, K., et al., *Degree of weight loss required to improve adipokine concentrations and decrease fat cell size in severely obese women.* Metabolism, 2009.
327. Anderson, J.W., et al., *Long-term weight-loss maintenance: a meta-analysis of US studies.* Am J Clin Nutr, 2001. **74**(5): p. 579-84.
328. Festa, A., et al., *The relation of body fat mass and distribution to markers of chronic inflammation.* Int J Obes Relat Metab Disord, 2001. **25**(10): p. 1407-15.
329. Snijder, M.B., et al., *What aspects of body fat are particularly hazardous and how do we measure them?* Int. J. Epidemiol., 2006. **35**(1): p. 83-92.
330. Arnlov, J., et al., *Impact of Body Mass Index and the Metabolic Syndrome on the Risk of Cardiovascular Disease and Death in Middle-Aged Men.* Circulation, 2009: p. CIRCULATIONAHA.109.887521.
331. Briel, M., et al., *Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis.* BMJ, 2009. **338**(feb16_1): p. b92-.
332. Kinosian, B., H. Glick, and G. Garland, *Cholesterol and Coronary Heart Disease: Predicting Risks by Levels and Ratios.* Annals of Internal Medicine, 1994. **121**(9): p. 641-647.
333. Perkins, G.M., et al., *Biomarkers of cardiovascular disease risk in 40-65-year-old men performing recommended levels of physical activity, compared with sedentary men.* Br J Sports Med, 2009. **43**(2): p. 136-141.
334. Nam, B.-H., W.B. Kannel, and R.B. D'Agostino, *Search for an Optimal Atherogenic Lipid Risk Profile: From the Framingham Study.* The American Journal of Cardiology, 2006. **97**(3): p. 372-375.
335. Sniderman, A.D., et al., *Errors that result from using the TC/HDL C ratio rather than the apoB/apoA-I ratio to identify the lipoprotein-related risk of vascular disease.* J Intern Med, 2006. **259**(5): p. 455-61.
336. Hennekens, C.H., et al., *Modest Dietary Reductions in Blood Cholesterol Have Important Public Health Benefits.* Journal of Cardiovascular Pharmacology and Therapeutics, 2009. **14**(2): p. 85-88.
337. Lin, C.Y., et al., *Effects of obesity, physical activity, and cardiorespiratory fitness on blood pressure, inflammation, and insulin resistance in the National Health and Nutrition Survey 1999-2002.* Nutr Metab Cardiovasc Dis, 2009.
338. Arsenault, B.J., et al., *Effect of exercise training on cardiometabolic risk markers among sedentary, but metabolically healthy overweight or obese post-menopausal women with elevated blood pressure.* Atherosclerosis, 2009. **207**(2): p. 530-533.
339. Elmer, P.J., et al., *Lifestyle Intervention: Results of the Treatment of Mild Hypertension Study (TOMHS).* Preventive Medicine, 1995. **24**(4): p. 378-388.
340. Staessen, J., R. Fagard, and A. Amery, *The relationship between body weight and blood pressure.* J Hum Hypertens, 1988. **2**(4): p. 207-17.
341. Stamler, J., et al., *INTERSALT study findings. Public health and medical care implications.* Hypertension, 1989. **14**(5): p. 570-7.
342. Hense, H.W., et al., *Framingham risk function overestimates risk of coronary heart disease in men and women from Germany--results from the MONICA Augsburg and the PROCAM cohorts.* Eur Heart J, 2003. **24**(10): p. 937-45.
343. Assmann, G., et al., *Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study.* Eur J Clin Invest, 2007. **37**(12): p. 925-32.

344. Assmann, G., H. Schulte, and U. Seedorf, *Cardiovascular risk assessment in the metabolic syndrome: results from the Prospective Cardiovascular Munster (PROCAM) Study.* Int J Obes (Lond), 2008. **32 Suppl 2**: p. S11-6.
345. Messier, V., et al., *Anthropometric, metabolic, psychosocial and dietary factors associated with dropout in overweight and obese postmenopausal women engaged in a 6-month weight loss programme: a MONET study.* Br J Nutr, 2009: p. 1-6.
346. Oja, P., et al., *Physical activity recommendations for health: what should Europe do?* BMC Public Health, 2010. **10**(1): p. 10.
347. Haskell, W.L., et al., *Physical Activity and Public Health. Updated Recommendation for Adults From the American College of Sports Medicine and the American Heart Association.* Circulation, 2007: p. CIRCULATIONAHA.107.185649.
348. Kruger, J., H.M. Blanck, and C. Gillespie, *Dietary and physical activity behaviors among adults successful at weight loss maintenance.* Int J Behav Nutr Phys Act, 2006. **3**(1): p. 17.
349. Nusselder, W., et al., *Living healthier for longer: Comparative effects of three heart-healthy behaviors on life expectancy with and without cardiovascular disease.* BMC Public Health, 2009. **9**(1): p. 487.
350. Lee, C.-D., X. Sui, and S.N. Blair, *Combined Effects of Cardiorespiratory Fitness, Not Smoking, and Normal Waist Girth on Morbidity and Mortality in Men.* Arch Intern Med, 2009. **169**(22): p. 2096-2101.
351. Bernard, C., *An Introduction to the Study of Experimental Medicine*. 1865.
352. Cannon, W.B., *ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS.* Physiol. Rev., 1929. **9**(3): p. 399-431.
353. McEwen, B.S. and J.C. Wingfield, *The concept of allostasis in biology and biomedicine.* Horm Behav, 2003. **43**(1): p. 2-15.
354. Nonogaki, K., *New insights into sympathetic regulation of glucose and fat metabolism.* Diabetologia, 2000. **43**(5): p. 533-49.

APPENDICES

APPENDIX 1 STATA PROTOCOLS

STATA Protocol for Table 2

```
. sampsi 0.75 0.6, alpha(0.05) onesample onesided

Estimated sample size for one-sample comparison of proportion to hypothesized value
Test Ho: p = 0.7500, where p is the proportion in the population
Assumptions:
         alpha =   0.0500  (one-sided)
         power =   0.9000
 alternative p =   0.6000
Estimated required sample size:
             n =       80


. sampsi 0 3.5, sd1(4) sd2(4) alpha(0.05) ratio(3) pre(1) post(1) r01(0.7) onesided
method(change)

Estimated sample size for two samples with repeated measures
Assumptions:
                                     alpha =   0.0500  (one-sided)
                                     power =   0.9000
                                        m1 =        0
                                        m2 =      3.5
                                       sd1 =        4
                                       sd2 =        4
                                     n2/n1 =     3.00
           number of follow-up measurements =        1
            number of baseline measurements =        1
   correlation between baseline & follow-up =    0.700
Method: CHANGE
 relative efficiency =    1.667
    adjustment to sd =    0.775
        adjusted sd1 =    3.098
        adjusted sd2 =    3.098

 Estimated required sample sizes:
                  n1 =        9
                  n2 =       27

. sampsi 0 3.5, sd1(4) sd2(4) alpha(0.05) n1(35) n2(85) pre(1) post(1) r01(0.7)
onesided method(change)

Estimated power for two samples with repeated measures
Assumptions:
                                     alpha =   0.0500  (one-sided)
                                        m1 =        0
                                        m2 =      3.5
                                       sd1 =        4
                                       sd2 =        4
                             sample size n1 =       35
                                        n2 =       85
                                     n2/n1 =     2.43
           number of follow-up measurements =        1
            number of baseline measurements =        1
   correlation between baseline & follow-up =    0.700
```

```
Method: CHANGE
 relative efficiency =    1.667
    adjustment to sd =    0.775
        adjusted sd1 =    3.098
        adjusted sd2 =    3.098
 Estimated power:
               power =    1.000

. sampsi 0 0.8, sd1(1.2) sd2(1.2) alpha(0.05) ratio(3) pre(1) post(1) r01(0.7)
onesided method(change)

Estimated sample size for two samples with repeated measures
Assumptions:
                                     alpha =   0.0500  (one-sided)
                                     power =   0.9000
                                        m1 =        0
                                        m2 =       .8
                                       sd1 =      1.2
                                       sd2 =      1.2
                                     n2/n1 =     3.00
           number of follow-up measurements =        1
            number of baseline measurements =        1
   correlation between baseline & follow-up =    0.700
Method: CHANGE
 relative efficiency =    1.667
    adjustment to sd =    0.775
        adjusted sd1 =    0.930
        adjusted sd2 =    0.930
 Estimated required sample sizes:
                  n1 =       16
                  n2 =       48

. sampsi 0 0.8, sd1(1.2) sd2(1.2) alpha(0.05) n1(35) n2(85) pre(1) post(1) r01(0.7)
onesided method(change)

Estimated power for two samples with repeated measures
Assumptions:
                                     alpha =   0.0500  (one-sided)
                                        m1 =        0
                                        m2 =       .8
                                       sd1 =      1.2
                                       sd2 =      1.2
                             sample size n1 =       35
                                        n2 =       85
                                     n2/n1 =     2.43
           number of follow-up measurements =        1
            number of baseline measurements =        1
   correlation between baseline & follow-up =    0.700
Method: CHANGE
 relative efficiency =    1.667
    adjustment to sd =    0.775
        adjusted sd1 =    0.930
        adjusted sd2 =    0.930
 Estimated power:
               power =    0.996
```

```
. sampsi 0 4, sd1(9) sd2(9) alpha(0.05) ratio(3) pre(1) post(1) r01(0.7) onesided
method(change)

Estimated sample size for two samples with repeated measures
Assumptions:
                                    alpha =   0.0500  (one-sided)
                                    power =   0.9000
                                       m1 =        0
                                       m2 =        4
                                      sd1 =        9
                                      sd2 =        9
                                    n2/n1 =     3.00
          number of follow-up measurements =        1
           number of baseline measurements =        1
   correlation between baseline & follow-up =    0.700
Method: CHANGE
 relative efficiency =    1.667
    adjustment to sd =    0.775
        adjusted sd1 =    6.971
        adjusted sd2 =    6.971
 Estimated required sample sizes:
                 n1 =       35
                 n2 =      105

. sampsi 0 4, sd1(9) sd2(9) alpha(0.05) n1(35) n2(85) pre(1) post(1) r01(0.7) onesided
method(change)

Estimated power for two samples with repeated measures
Assumptions:
                                    alpha =   0.0500  (one-sided)
                                       m1 =        0
                                       m2 =        4
                                      sd1 =        9
                                      sd2 =        9
                           sample size n1 =       35
                                       n2 =       85
                                    n2/n1 =     2.43
          number of follow-up measurements =        1
           number of baseline measurements =        1
   correlation between baseline & follow-up =    0.700
Method: CHANGE
 relative efficiency =    1.667
    adjustment to sd =    0.775
        adjusted sd1 =    6.971
        adjusted sd2 =    6.971
 Estimated power:
              power =    0.887
```

STATA Protocol for Table 4a

```
. by cflstatus_adj, sort : summarize age1 weight1 bmi1 percent_fat1 vo2peakpweight1
tch1 hdl1 ldl1 tch_hdl1 tg1 syst1 dia1 procam_risk1


-> cflstatus_adj = inactive
    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
        age1 |        28    48.28571    7.551586         27         58
     weight1 |        28      92.975    13.57644         71      118.1
        bmi1 |        28    29.77857    4.420856       23.1       41.4
percent_fat1 |        28    28.69002     8.18574   16.00512   47.66607
vo2peakpwe~1 |        28    31.76539     7.70059   18.69838   51.76687
-------------+--------------------------------------------------------
        tch1 |        28    221.2143    54.52445        119        355
        hdl1 |        28      55.175    16.33215         26         89
        ldl1 |        28    137.3107    47.45202       41.4        255
    tch_hdl1 |        28    4.218355    1.152234   2.333333   6.371428
         tg1 |        28    143.6429     71.6877         47        333
-------------+--------------------------------------------------------
       syst1 |        27    136.0741    11.95802        115        162
        dia1 |        27    82.88889    8.491323         67         98
procam_risk1 |        27    3.756808    4.649846   .0092389   20.78417

-> cflstatus_adj = active
    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
        age1 |        89    50.44944    9.648376         25         72
     weight1 |        89    86.67528    15.02062       56.8      120.6
        bmi1 |        89    28.57978    4.037809       19.9       41.7
percent_fat1 |        89    28.87336    7.459166         10   48.65546
vo2peakpwe~1 |        89    31.97881    8.108567   14.79339   52.35294
-------------+--------------------------------------------------------
        tch1 |        87     223.977    49.10832         87        370
        hdl1 |        87    54.45977    12.97296         32        105
        ldl1 |        87    138.4667    44.58913       36.6      274.2
    tch_hdl1 |        87    4.270923    1.153065   2.023256   7.619048
         tg1 |        87    155.2529    104.8056         37        748
-------------+--------------------------------------------------------
       syst1 |        83    142.5181    16.27235        112        191
        dia1 |        83    82.75904    9.956724         57        108
procam_risk1 |        82    5.159766    6.537022   .0005913   38.28459
```

STATA Protocol for Table 7

```
-> cflstatus_adj = inactive
Paired t test
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
vo2peak1 |      23    32.51456     1.66091    7.965444    29.07004  35.95907
vo2peak2 |      23    32.09135    1.652626    7.925716    28.66401  35.51869
---------+--------------------------------------------------------------------
    diff |      23    .4232075    .4705596    2.256725   -.5526734  1.399088
------------------------------------------------------------------------------
     mean(diff) = mean(vo2peakpweight1 - vo2peakpweight9)         t =   0.8994
 Ho: mean(diff) = 0                              degrees of freedom =       22

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8109         Pr(|T| > |t|) = 0.3782          Pr(T > t) = 0.1891

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
vo2peak1 |      73     32.7894    .9466564    8.088236    30.90227    34.67652
vo2peak2 |      73    36.13564      1.0843     9.26426    33.97413    38.29715
---------+--------------------------------------------------------------------
    diff |      73   -3.346244    .4691694    4.008585   -4.281516   -2.410971
------------------------------------------------------------------------------
     mean(diff) = mean(vo2peakpweight1 - vo2peakpweight9)         t =  -7.1323
 Ho: mean(diff) = 0                              degrees of freedom =       72

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23   -.4232075    .4705596    2.256725   -1.399088    .5526734
  active |      73    3.346244    .4691694    4.008585    2.410971    4.281516
---------+--------------------------------------------------------------------
combined |      96    2.443146    .4079121    3.996706    1.633338    3.252954
---------+--------------------------------------------------------------------
    diff |           -3.769451    .8785688               -5.51387   -2.025032
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -4.2904
Ho: diff = 0                                    degrees of freedom =       94

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
```

STATA Protocol For Table 8

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
VO2/BCM1 |      23    85.12461    2.937223    14.08643    79.03318    91.21604
VO2/BCM2 |      23    83.25456    2.937826    14.08932    77.16188    89.34724
---------+--------------------------------------------------------------------
    diff |      23    1.870049     1.30982    6.281674   -.8463501    4.586449
------------------------------------------------------------------------------
     mean(diff) = mean(vo2peakpbcm1 - vo2peakpbcm9)               t =   1.4277
 Ho: mean(diff) = 0                                degrees of freedom =       22

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9163         Pr(|T| > |t|) = 0.1674          Pr(T > t) = 0.0837

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
VO2/BCM1 |      73    86.78714    1.887497    16.12678    83.02448    90.54979
VO2/BCM2 |      73    92.10266    1.935488    16.53682    88.24433    95.96098
---------+--------------------------------------------------------------------
    diff |      73   -5.315524    1.040199    8.887467   -7.389124   -3.241925
------------------------------------------------------------------------------
     mean(diff) = mean(vo2peakpbcm1 - vo2peakpbcm9)               t =  -5.1101
 Ho: mean(diff) = 0                                degrees of freedom =       72

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23   -1.870049     1.30982    6.281674   -4.586449    .8463501
  active |      73    5.315524    1.040199    8.887467    3.241925    7.389124
---------+--------------------------------------------------------------------
combined |      96    3.593981    .9043151    8.860442    1.798688    5.389273
---------+--------------------------------------------------------------------
    diff |           -7.185574    1.996818               -11.1503   -3.220844
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -3.5985
Ho: diff = 0                                     degrees of freedom =       94

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0003         Pr(|T| > |t|) = 0.0005          Pr(T > t) = 0.9997
```

STATA Protocol For Table 9

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
VO2peak1 |      23    32.51456     1.66091    7.965444    29.07004    35.95907
VO2peak2 |      23    32.09135    1.652626    7.925716    28.66401    35.51869
---------+--------------------------------------------------------------------
    diff |      23    .4232075    .4705596    2.256725   -.5526734    1.399088
------------------------------------------------------------------------------
     mean(diff) = mean(vo2peakpweight1 - vo2peakpweight9)         t =   0.8994
 Ho: mean(diff) = 0                              degrees of freedom =       22

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8109         Pr(|T| > |t|) = 0.3782          Pr(T > t) = 0.1891

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
VO2peak1 |      71    32.68572    .9683816    8.159728    30.75434    34.61709
VO2peak2 |      71    35.71592     1.07049     9.02011     33.5809    37.85095
---------+--------------------------------------------------------------------
    diff |      71   -3.030205    .4250104    3.581201   -3.877861   -2.182548
------------------------------------------------------------------------------
     mean(diff) = mean(vo2peakpweight1 - vo2peakpweight9)         t =  -7.1297
 Ho: mean(diff) = 0                              degrees of freedom =       70

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000


Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23   -.4232075    .4705596    2.256725   -1.399088    .5526734
  active |      71    3.030205    .4250104    3.581201    2.182548    3.877861
---------+--------------------------------------------------------------------
combined |      94    2.185221    .3731088    3.617424    1.444301    2.926141
---------+--------------------------------------------------------------------
    diff |           -3.453412     .794864               -5.032081   -1.874743
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -4.3447
Ho: diff = 0                                    degrees of freedom =       92

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
```

STATA Protocol For Table 10

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    male |      72    35.41231    .8081056    6.857004      33.801    37.02363
  female |      29     25.3562    1.003456    5.403778    23.30071    27.41169
---------+--------------------------------------------------------------------
combined |     101    32.52492    .7864275    7.903498    30.96467    34.08517
---------+--------------------------------------------------------------------
    diff |            10.05611    1.424991                7.228621    12.88361
------------------------------------------------------------------------------
    diff = mean(male) - mean(female)                              t =   7.0570
Ho: diff = 0                                     degrees of freedom =       99

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000


Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    male |      72    88.45455    1.831318    15.53925      84.803    92.10609
  female |      29    81.14998    2.555582    13.76223    75.91511    86.38485
---------+--------------------------------------------------------------------
combined |     101     86.3572    1.527001    15.34617    83.32767    89.38672
---------+--------------------------------------------------------------------
    diff |            7.304569    3.311777                .733285    13.87585
------------------------------------------------------------------------------
    diff = mean(male) - mean(female)                              t =   2.2056
Ho: diff = 0                                     degrees of freedom =       99

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9851         Pr(|T| > |t|) = 0.0297          Pr(T > t) = 0.0149
```

STATA Log for Table 11

```
CFL90 Strata
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23    1.092901    .0407071    .1952243    1.008479    1.177322
  active |      73    1.150922    .0256102     .218814    1.099869    1.201975
---------+--------------------------------------------------------------------
combined |      96    1.137021    .0218264     .213854     1.09369    1.180352
---------+--------------------------------------------------------------------
    diff |           -.0580217    .0510579               -.1593983    .0433549
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -1.1364
Ho: diff = 0                                     degrees of freedom =       94
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.1293         Pr(|T| > |t|) = 0.2587          Pr(T > t) = 0.8707

CFL120 Strata
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |      26    1.097781    .0411152    .2096471    1.013102    1.182459
       1 |      70    1.151596    .0257033    .2150491     1.10032    1.202873
---------+--------------------------------------------------------------------
combined |      96    1.137021    .0218264     .213854     1.09369    1.180352
---------+--------------------------------------------------------------------
    diff |           -.0538156    .0490629               -.1512312    .0435999
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =  -1.0969
Ho: diff = 0                                     degrees of freedom =       94
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.1378         Pr(|T| > |t|) = 0.2755          Pr(T > t) = 0.8622

CFL150 Strata
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |      42    1.120636    .0329983    .2138536    1.053995    1.187278
       1 |      54    1.149765    .0292557    .2149844    1.091085    1.208444
---------+--------------------------------------------------------------------
combined |      96    1.137021    .0218264     .213854     1.09369    1.180352
---------+--------------------------------------------------------------------
    diff |           -.0291284    .0441291               -.1167477     .058491
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =  -0.6601
Ho: diff = 0                                     degrees of freedom =       94
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.2554         Pr(|T| > |t|) = 0.5108          Pr(T > t) = 0.7446
```

STATA Protocol For Table 12

CFL90 Strata

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23   -.0133943    .0161481    .0774436   -.0468834    .0200948
  active |      73    .1160251    .0162604    .1389287    .0836106    .1484395
---------+--------------------------------------------------------------------
combined |      96    .0850184    .0141055    .1382054    .0570153    .1130214
---------+--------------------------------------------------------------------
    diff |           -.1294194    .0304229               -.1898248   -.0690139
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -4.2540
Ho: diff = 0                                     degrees of freedom =       94
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
```

CFL120 Strata

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      26    .0083206    .0187448      .09558    -.030285    .0469262
  active |      70    .1135061    .0168812    .1412381    .0798291    .1471832
---------+--------------------------------------------------------------------
combined |      96    .0850184    .0141055    .1382054    .0570153    .1130214
---------+--------------------------------------------------------------------
    diff |           -.1051855    .0300088               -.1647687   -.0456024
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =  -3.5052
Ho: diff = 0                                     degrees of freedom =       94
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0004         Pr(|T| > |t|) = 0.0007          Pr(T > t) = 0.9996
```

CFL150 Strata

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      42    .0342825    .0205733    .1333303   -.0072662    .0758311
  active |      54    .1244796    .0176691    .1298412    .0890398    .1599194
---------+--------------------------------------------------------------------
combined |      96    .0850184    .0141055    .1382054    .0570153    .1130214
---------+--------------------------------------------------------------------
    diff |           -.0901972    .0270287               -.1438632   -.0365311
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =  -3.3371
Ho: diff = 0                                     degrees of freedom =       94

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0006         Pr(|T| > |t|) = 0.0012          Pr(T > t) = 0.9994
```

STATA Protocol For Table 13

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ |   VO2change
       adj |         0          1 |     Total
-----------+----------------------+----------
  inactive |        23          0 |        23
           |      15.3        7.7 |      23.0
           |    100.00       0.00 |    100.00
-----------+----------------------+----------
    active |        41         32 |        73
           |      48.7       24.3 |      73.0
           |     56.16      43.84 |    100.00
-----------+----------------------+----------
     Total |        64         32 |        96
           |      64.0       32.0 |      96.0
           |     66.67      33.33 |    100.00

          Pearson chi2(1) =  15.1233   Pr = 0.000
           Fisher's exact =                 0.000
   1-sided Fisher's exact =                 0.000

+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus1 |   VO2change
         6 |         0          1 |     Total
-----------+----------------------+----------
         0 |        23          3 |        26
           |      17.3        8.7 |      26.0
           |     88.46      11.54 |    100.00
-----------+----------------------+----------
         1 |        41         29 |        70
           |      46.7       23.3 |      70.0
           |     58.57      41.43 |    100.00
-----------+----------------------+----------
     Total |        64         32 |        96
           |      64.0       32.0 |      96.0
           |     66.67      33.33 |    100.00

          Pearson chi2(1) =   7.6220   Pr = 0.006
           Fisher's exact =                 0.007
   1-sided Fisher's exact =                 0.004
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus2 |   VO2change
         0 |         0          1 |     Total
-----------+----------------------+----------
         0 |        34          8 |        42
           |      28.0       14.0 |      42.0
           |     80.95      19.05 |    100.00
-----------+----------------------+----------
         1 |        30         24 |        54
           |      36.0       18.0 |      54.0
           |     55.56      44.44 |    100.00
-----------+----------------------+----------
     Total |        64         32 |        96
           |      64.0       32.0 |      96.0
           |     66.67      33.33 |    100.00

          Pearson chi2(1) =   6.8571   Pr = 0.009
           Fisher's exact =                 0.010
   1-sided Fisher's exact =                 0.007


Logistic regression                               Number of obs   =         96
                                                  LR chi2(1)      =       8.64
                                                  Prob > chi2     =     0.0033
Log likelihood = -56.784939                       Pseudo R2       =     0.0707

------------------------------------------------------------------------------
vo2peakpw~35 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cflstatus16 |   5.422764   3.579372     2.56   0.010     1.487213    19.77281
------------------------------------------------------------------------------

. logistic VO2changecflstatus20 if study==0 & vo2peakvalid1==0 & vo2peakvalid9==0 &
vo2peakpweightp!=.

Logistic regression                               Number of obs   =         96
                                                  LR chi2(1)      =       7.12
                                                  Prob > chi2     =     0.0076
Log likelihood = -57.546259                       Pseudo R2       =     0.0582

------------------------------------------------------------------------------
vo2peakpw~35 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cflstatus20 |        3.4   1.628496     2.56   0.011     1.329779    8.693176
------------------------------------------------------------------------------
```

STATA Protocol For Table 14

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 weight1 |      24    94.15833    2.782502    13.63142    88.40229    99.91438
 weight2 |      24    92.62083    2.479145    12.14528    87.49233    97.74933
---------+--------------------------------------------------------------------
    diff |      24      1.5375    .5581676    2.734452    .3828421    2.692157
------------------------------------------------------------------------------
     mean(diff) = mean(weight1 - weight9)                         t =   2.7545
 Ho: mean(diff) = 0                             degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9944         Pr(|T| > |t|) = 0.0113          Pr(T > t) = 0.0056

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 weight1 |      73    90.80137    1.529061     13.0643    87.75324     93.8495
 weight2 |      73    86.47534    1.451398    12.40075    83.58203    89.36865
---------+--------------------------------------------------------------------
    diff |      73    4.326027    .5901366    5.042129    3.149612    5.502443
------------------------------------------------------------------------------
     mean(diff) = mean(weight1 - weight9)                         t =   7.3306
 Ho: mean(diff) = 0                             degrees of freedom =       72

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24     -1.5375    .5581676    2.734452   -2.692157   -.3828421
  active |      73   -4.326027    .5901366    5.042129   -5.502443   -3.149612
---------+--------------------------------------------------------------------
combined |      97   -3.636082     .479709    4.724585   -4.588297   -2.683868
---------+--------------------------------------------------------------------
    diff |            2.788528     1.08028                .6439002    4.933155
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.5813
Ho: diff = 0                                     degrees of freedom =       95

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9943         Pr(|T| > |t|) = 0.0114          Pr(T > t) = 0.0057
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    bmi1 |      24    30.38333    .8790984    4.306685    28.56478    32.20189
    bmi2 |      24      29.925    .8065235    3.951142    28.25658    31.59342
---------+--------------------------------------------------------------------
    diff |      24    .4583331    .1811713    .8875547    .0835516    .8331146
------------------------------------------------------------------------------
     mean(diff) = mean(bmi1 - bmi9)                               t =   2.5298
 Ho: mean(diff) = 0                             degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9906         Pr(|T| > |t|) = 0.0187          Pr(T > t) = 0.0094

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    bmi1 |      73    29.75616     .398131    3.401633     28.9625    30.54982
    bmi2 |      73    28.34795    .3901231    3.333213    27.57025    29.12564
---------+--------------------------------------------------------------------
    diff |      73    1.408219    .1921178    1.641455    1.025239    1.791199
------------------------------------------------------------------------------
     mean(diff) = mean(bmi1 - bmi9)                               t =   7.3300
 Ho: mean(diff) = 0                             degrees of freedom =       72

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -.4583331    .1811713    .8875547   -.8331146   -.0835516
  active |      73   -1.408219    .1921178    1.641455   -1.791199   -1.025239
---------+--------------------------------------------------------------------
combined |      97   -1.173196    .1566161    1.542489   -1.484076   -.8623153
---------+--------------------------------------------------------------------
    diff |             .949886    .3515937                .2518844    1.647888
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.7017
Ho: diff = 0                                    degrees of freedom =       95

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9959         Pr(|T| > |t|) = 0.0082          Pr(T > t) = 0.0041
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 fat_kg1 |      24    28.60417    2.054506    10.06498     24.3541    32.85424
 fat_kg2 |      24    27.39583    1.860346    9.113796    23.54741    31.24425
---------+--------------------------------------------------------------------
    diff |      24    1.208333      .43924    2.151828    .2996958     2.11697
------------------------------------------------------------------------------
     mean(diff) = mean(fat_kg1 - fat_kg9)                         t =   2.7510
 Ho: mean(diff) = 0                              degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9943         Pr(|T| > |t|) = 0.0114          Pr(T > t) = 0.0057

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 fat_kg1 |      73    27.37397    .9559018    8.167228    25.46842    29.27953
 fat_kg2 |      73    24.09178    .9667666    8.260057    22.16457    26.01899
---------+--------------------------------------------------------------------
    diff |      73    3.282192     .442145    3.777688    2.400792    4.163592
------------------------------------------------------------------------------
     mean(diff) = mean(fat_kg1 - fat_kg9)                         t =   7.4233
 Ho: mean(diff) = 0                              degrees of freedom =       72

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -1.208333      .43924    2.151828   -2.11697   -.2996958
  active |      73   -3.282192     .442145    3.777688   -4.163592   -2.400792
---------+--------------------------------------------------------------------
combined |      97   -2.769072    .3607229    3.552709   -3.485101   -2.053043
---------+--------------------------------------------------------------------
    diff |            2.073859    .8129513                .4599465    3.687771
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.5510
Ho: diff = 0                                     degrees of freedom =       95

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9938         Pr(|T| > |t|) = 0.0123          Pr(T > t) = 0.0062
```

STATA Protocol For Table 15

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 weight1 |      24    94.15833    2.782502    13.63142    88.40229    99.91438
 weight2 |      24    92.62083    2.479145    12.14528    87.49233    97.74933
---------+--------------------------------------------------------------------
    diff |      24      1.5375    .5581676    2.734452    .3828421    2.692157
------------------------------------------------------------------------------
     mean(diff) = mean(weight1 - weight9)                         t =   2.7545
 Ho: mean(diff) = 0                              degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9944         Pr(|T| > |t|) = 0.0113          Pr(T > t) = 0.0056

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 weight1 |      70    90.16429    1.530661    12.80643     87.1107    93.21787
 weight2 |      70       86.51    1.492079    12.48363    83.53338    89.48662
---------+--------------------------------------------------------------------
    diff |      70    3.654286    .4398366    3.679937    2.776836    4.531736
------------------------------------------------------------------------------
     mean(diff) = mean(weight1 - weight9)                         t =   8.3083
 Ho: mean(diff) = 0                              degrees of freedom =       69

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24     -1.5375    .5581676    2.734452   -2.692157   -.3828421
  active |      70    -3.654286    .4398366    3.679937   -4.531736   -2.776836
---------+--------------------------------------------------------------------
combined |      94    -3.11383       .3684    3.571771   -3.845399    -2.38226
---------+--------------------------------------------------------------------
    diff |            2.116786    .8202864                .4876262    3.745946
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.5805
Ho: diff = 0                                     degrees of freedom =       92

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9943         Pr(|T| > |t|) = 0.0114          Pr(T > t) = 0.0057
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    bmi1 |      24    30.38333    .8790984    4.306685    28.56478    32.20189
    bmi2 |      24      29.925    .8065235    3.951142    28.25658    31.59342
---------+--------------------------------------------------------------------
    diff |      24    .4583331    .1811713    .8875547    .0835516    .8331146
------------------------------------------------------------------------------
     mean(diff) = mean(bmi1 - bmi9)                               t =   2.5298
 Ho: mean(diff) = 0                             degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9906         Pr(|T| > |t|) = 0.0187          Pr(T > t) = 0.0094

------------------------------------------------------------------------------------------------
---------------------------------
-> cflstatus_adj = active

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    bmi1 |      70    29.57143     .383992    3.212708    28.80539    30.33747
    bmi2 |      70    28.38143    .3937466    3.294321    27.59593    29.16693
---------+--------------------------------------------------------------------
    diff |      70        1.19    .1406455    1.176725    .9094199     1.47058
------------------------------------------------------------------------------
     mean(diff) = mean(bmi1 - bmi9)                               t =   8.4610
 Ho: mean(diff) = 0                             degrees of freedom =       69

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -.4583331    .1811713    .8875547   -.8331146   -.0835516
  active |      70       -1.19    .1406455    1.176725    -1.47058   -.9094199
---------+--------------------------------------------------------------------
combined |      94   -1.003191    .1187274    1.151105   -1.238961   -.7674222
---------+--------------------------------------------------------------------
    diff |            .7316669    .2629189                .2094874    1.253846
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.7829
Ho: diff = 0                                    degrees of freedom =       92

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9967         Pr(|T| > |t|) = 0.0065          Pr(T > t) = 0.0033
```

```
-> cflstatus_adj = inactive

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 fat_kg1 |      24    28.60417    2.054506    10.06498     24.3541    32.85424
 fat_kg2 |      24    27.39583    1.860346    9.113796    23.54741    31.24425
---------+--------------------------------------------------------------------
    diff |      24    1.208333      .43924    2.151828    .2996958     2.11697
------------------------------------------------------------------------------
     mean(diff) = mean(fat_kg1 - fat_kg9)                         t =   2.7510
 Ho: mean(diff) = 0                              degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9943         Pr(|T| > |t|) = 0.0114          Pr(T > t) = 0.0057

------------------------------------------------------------------------------------------------
---------------------------------
-> cflstatus_adj = active

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 fat_kg1 |      70    27.16571    .9782371    8.184519    25.21418    29.11724
 fat_kg2 |      70    24.39571     .981663    8.213182    22.43735    26.35408
---------+--------------------------------------------------------------------
    diff |      70        2.77    .3235629    2.707122     2.12451     3.41549
------------------------------------------------------------------------------
     mean(diff) = mean(fat_kg1 - fat_kg9)                         t =   8.5609
 Ho: mean(diff) = 0                              degrees of freedom =       69

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -1.208333      .43924    2.151828    -2.11697   -.2996958
  active |      70       -2.77    .3235629    2.707122    -3.41549    -2.12451
---------+--------------------------------------------------------------------
combined |      94   -2.371277    .2738827    2.655391   -2.915153     -1.8274
---------+--------------------------------------------------------------------
    diff |            1.561667    .6101684                .3498199    2.773514
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.5594
Ho: diff = 0                                    degrees of freedom =       92

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9939         Pr(|T| > |t|) = 0.0121          Pr(T > t) = 0.0061
```

STATA Protocol For Table 16

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ |    weightloss≥5%
       adj |         0          1 |     Total
-----------+----------------------+----------
  inactive |        22          2 |        24
           |      15.8        8.2 |      24.0
           |     91.67       8.33 |    100.00
-----------+----------------------+----------
    active |        42         31 |        73
           |      48.2       24.8 |      73.0
           |     57.53      42.47 |    100.00
-----------+----------------------+----------
     Total |        64         33 |        97
           |      64.0       33.0 |      97.0
           |     65.98      34.02 |    100.00

          Pearson chi2(1) =   9.3745   Pr = 0.002
           Fisher's exact =                 0.002
   1-sided Fisher's exact =                 0.001

Logistic regression                               Number of obs   =         97
                                                  LR chi2(1)      =      11.08
                                                  Prob > chi2     =     0.0009
Log likelihood = -56.651875                       Pseudo R2       =     0.0891

------------------------------------------------------------------------------
weightloss   | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cfl          |   8.119047   6.296959     2.70   0.007     1.775544    37.12605
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus1 | weightloss≥5%
         6 |         0          1 |     Total
-----------+----------------------+----------
         0 |        23          4 |        27
           |      17.8        9.2 |      27.0
           |     85.19      14.81 |    100.00
-----------+----------------------+----------
         1 |        41         29 |        70
           |      46.2       23.8 |      70.0
           |     58.57      41.43 |    100.00
-----------+----------------------+----------
     Total |        64         33 |        97
           |      64.0       33.0 |      97.0
           |     65.98      34.02 |    100.00

          Pearson chi2(1) =   6.1483   Pr = 0.013
           Fisher's exact =                 0.016
   1-sided Fisher's exact =                 0.010


Logistic regression                               Number of obs   =         97
                                                  LR chi2(1)      =       6.76
                                                  Prob > chi2     =     0.0093
Log likelihood = -58.812684                       Pseudo R2       =     0.0544

------------------------------------------------------------------------------
weightloss   | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cfl         |   4.067073   2.414181     2.36   0.018      1.27062    13.01812
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus2 | weightloss≥5%
         0 |         0          1 |     Total
-----------+----------------------+----------
         0 |        34          9 |        43
           |      28.4       14.6 |      43.0
           |     79.07      20.93 |    100.00
-----------+----------------------+----------
         1 |        30         24 |        54
           |      35.6       18.4 |      54.0
           |     55.56      44.44 |    100.00
-----------+----------------------+----------
     Total |        64         33 |        97
           |      64.0       33.0 |      97.0
           |     65.98      34.02 |    100.00

          Pearson chi2(1) =   5.8966   Pr = 0.015
           Fisher's exact =                 0.018
   1-sided Fisher's exact =                 0.013

. logistic weightchange05 cflstatus20 if study==0 & bmi1>25 & bmi1!=. & bmi9!=.

Logistic regression                               Number of obs   =         97
                                                  LR chi2(1)      =       6.07
                                                  Prob > chi2     =     0.0137
Log likelihood = -59.156251                       Pseudo R2       =     0.0488

------------------------------------------------------------------------------
weightloss   | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 cfl         |   3.022222    1.40305     2.38   0.017     1.216636    7.507441
------------------------------------------------------------------------------
```

STATA Protocol For Table17a

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    TCH1 |      23     225.913    11.34509    54.40915    202.3848    249.4413
    TCH2 |      23    228.4783    11.72576    56.23479    204.1605     252.796
---------+--------------------------------------------------------------------
    diff |      23   -2.565217    4.829842    23.16311    -12.5817    7.451262
------------------------------------------------------------------------------
     mean(diff) = mean(tch1 - tch9)                               t =  -0.5311
 Ho: mean(diff) = 0                             degrees of freedom =       22

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.3003         Pr(|T| > |t|) = 0.6007          Pr(T > t) = 0.6997

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    TCH1 |      87     223.977    5.264965    49.10832    213.5106    234.4434
    TCH2 |      87         215     4.93505    46.03108    205.1894    224.8106
---------+--------------------------------------------------------------------
    diff |      87    8.977011    2.561459     23.8917    3.884999    14.06902
------------------------------------------------------------------------------
     mean(diff) = mean(tch1 - tch9)                               t =   3.5046
 Ho: mean(diff) = 0                             degrees of freedom =       86

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9996         Pr(|T| > |t|) = 0.0007          Pr(T > t) = 0.0004

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23   -2.565217    4.829842    23.16311    -12.5817    7.451262
  active |      87    8.977011    2.561459     23.8917    3.884999    14.06902
---------+--------------------------------------------------------------------
combined |     110    6.563636    2.298004    24.10167    2.009067    11.11821
---------+--------------------------------------------------------------------
    diff |           -11.54223    5.567327               -22.57764     -.50682
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -2.0732
Ho: diff = 0                                     degrees of freedom =      108

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0203         Pr(|T| > |t|) = 0.0405          Pr(T > t) = 0.9797
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    TCH1 |      17    247.7647    10.72159    44.20623     225.036    270.4935
    TCH2 |      17    250.1765    11.33391    46.73093    226.1496    274.2033
---------+--------------------------------------------------------------------
    diff |      17   -2.411765    6.397988    26.37958   -15.97489    11.15136
------------------------------------------------------------------------------
     mean(diff) = mean(tch1 - tch9)                               t =  -0.3770
 Ho: mean(diff) = 0                             degrees of freedom =       16

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.3556         Pr(|T| > |t|) = 0.7112          Pr(T > t) = 0.6444

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    TCH1 |      67    241.3582    4.810836    39.37839    231.7531    250.9634
    TCH2 |      67    229.7761    4.811453    39.38344    220.1697    239.3825
---------+--------------------------------------------------------------------
    diff |      67    11.58209    3.105862    25.42258    5.381035    17.78314
------------------------------------------------------------------------------
     mean(diff) = mean(tch1 - tch9)                               t =   3.7291
 Ho: mean(diff) = 0                             degrees of freedom =       66

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9998         Pr(|T| > |t|) = 0.0004          Pr(T > t) = 0.0002

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      17   -2.411765    6.397988    26.37958   -15.97489    11.15136
  active |      67    11.58209    3.105862    25.42258    5.381035    17.78314
---------+--------------------------------------------------------------------
combined |      84        8.75    2.845358    26.07814    3.090697     14.4093
---------+--------------------------------------------------------------------
    diff |           -13.99385    6.955419               -27.8304   -.1573099
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -2.0119
Ho: diff = 0                                   degrees of freedom =       82

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0238         Pr(|T| > |t|) = 0.0475          Pr(T > t) = 0.9762
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    hdl1 |      24    57.20417    3.338459    16.35504    50.29804    64.11029
    hdl2 |      24      55.875    3.167608    15.51805     49.3223     62.4277
---------+--------------------------------------------------------------------
    diff |      24    1.329167    1.345827    6.593177   -1.454888    4.113221
------------------------------------------------------------------------------
     mean(diff) = mean(hdl1 - hdl9)                               t =   0.9876
 Ho: mean(diff) = 0                             degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8332         Pr(|T| > |t|) = 0.3336          Pr(T > t) = 0.1668

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    hdl1 |      87    54.45977    1.390848    12.97296    51.69486    57.22468
    hdl2 |      87     55.4023    1.293731    12.06712    52.83045    57.97415
---------+--------------------------------------------------------------------
    diff |      87   -.9425287    .7736914    7.216513   -2.480576    .5955188
------------------------------------------------------------------------------
     mean(diff) = mean(hdl1 - hdl9)                               t =  -1.2182
 Ho: mean(diff) = 0                             degrees of freedom =       86

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.1132         Pr(|T| > |t|) = 0.2265          Pr(T > t) = 0.8868

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -1.329167    1.345827    6.593177   -4.113221    1.454888
  active |      87    .9425287    .7736914    7.216513   -.5955188    2.480576
---------+--------------------------------------------------------------------
combined |     111    .4513513    .6757528    7.119498   -.8878321    1.790535
---------+--------------------------------------------------------------------
    diff |           -2.271695    1.634612               -5.511443    .9680525
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -1.3897
Ho: diff = 0                                    degrees of freedom =      109

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0837         Pr(|T| > |t|) = 0.1674          Pr(T > t) = 0.9163
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    hdl1 |      18        54.5    3.572087    15.15508    46.96356    62.03644
    hdl2 |      18    53.61111    3.602957    15.28605    46.00954    61.21269
---------+--------------------------------------------------------------------
    diff |      18    .8888889    1.516551    6.434182   -2.310754    4.088532
------------------------------------------------------------------------------
     mean(diff) = mean(hdl1 - hdl9)                               t =   0.5861
 Ho: mean(diff) = 0                             degrees of freedom =       17

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.7173         Pr(|T| > |t|) = 0.5655          Pr(T > t) = 0.2827

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    hdl1 |      62    50.16129    1.158098    9.118875    47.84553    52.47705
    hdl2 |      62    52.48387    1.263895     9.95192    49.95656    55.01119
---------+--------------------------------------------------------------------
    diff |      62   -2.322581    .8612875    6.781784   -4.044831   -.6003299
------------------------------------------------------------------------------
     mean(diff) = mean(hdl1 - hdl9)                               t =  -2.6966
 Ho: mean(diff) = 0                             degrees of freedom =       61

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0045         Pr(|T| > |t|) = 0.0090          Pr(T > t) = 0.9955

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      18   -.8888889    1.516551    6.434182   -4.088532    2.310754
  active |      62    2.322581    .8612875    6.781784    .6003299    4.044831
---------+--------------------------------------------------------------------
combined |      80         1.6    .7602881    6.800223    .0866844    3.113316
---------+--------------------------------------------------------------------
    diff |            -3.21147    1.795881               -6.786793    .3638541
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -1.7882
Ho: diff = 0                                    degrees of freedom =       78

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0388         Pr(|T| > |t|) = 0.0776          Pr(T > t) = 0.9612
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tch/hdl1 |      23    4.178725    .2422847    1.161956    3.676258    4.681193
tch/hdl2 |      23    4.290586    .2503259    1.200521    3.771442     4.80973
---------+--------------------------------------------------------------------
    diff |      23   -.1118606    .1221191    .5856626   -.3651201    .1413989
------------------------------------------------------------------------------
     mean(diff) = mean(tch_hdl1 - tch_hdl9)                       t =  -0.9160
 Ho: mean(diff) = 0                               degrees of freedom =       22

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.1848         Pr(|T| > |t|) = 0.3696          Pr(T > t) = 0.8152

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tch/hdl1 |      87    4.270923    .1236215    1.153065    4.025172    4.516675
tch/hdl2 |      87    4.034917    .1136416    1.059978    3.809005    4.260829
---------+--------------------------------------------------------------------
    diff |      87    .2360062    .0648678    .6050464    .1070534    .3649591
------------------------------------------------------------------------------
     mean(diff) = mean(tch_hdl1 - tch_hdl9)                       t =   3.6383
 Ho: mean(diff) = 0                               degrees of freedom =       86

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9998         Pr(|T| > |t|) = 0.0005          Pr(T > t) = 0.0002

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23    .1118606    .1221191    .5856626   -.1413989    .3651201
  active |      87   -.2360062    .0648678    .6050464   -.3649591   -.1070534
---------+--------------------------------------------------------------------
combined |     110   -.1632704    .0586406    .6150281   -.2794943   -.0470466
---------+--------------------------------------------------------------------
    diff |            .3478669    .1409466                .0684863    .6272475
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.4681
Ho: diff = 0                                     degrees of freedom =      108

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9924         Pr(|T| > |t|) = 0.0152          Pr(T > t) = 0.0076
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tch/hdl1 |      12    5.049463    .2419347    .8380863    4.516968    5.581958
tch/hdl2 |      12    5.120836    .2656228    .9201445    4.536204    5.705468
---------+--------------------------------------------------------------------
    diff |      12   -.0713727    .1561417    .5408908   -.4150383     .272293
------------------------------------------------------------------------------
     mean(diff) = mean(tch_hdl1 - tch_hdl9)                      t =  -0.4571
 Ho: mean(diff) = 0                               degrees of freedom =       11

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.3282         Pr(|T| > |t|) = 0.6565          Pr(T > t) = 0.6718

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tch/hdl1 |      51    5.033791    .1144265    .8171685    4.803959    5.263623
tch/hdl2 |      51     4.61454    .1273608    .9095384    4.358728    4.870351
---------+--------------------------------------------------------------------
    diff |      51    .4192513    .0928977    .6634224    .2326608    .6058419
------------------------------------------------------------------------------
     mean(diff) = mean(tch_hdl1 - tch_hdl9)                      t =   4.5130
 Ho: mean(diff) = 0                               degrees of freedom =       50

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      12    .0713727    .1561417    .5408908    -.272293    .4150383
  active |      51   -.4192513    .0928977    .6634224   -.6058419   -.2326608
---------+--------------------------------------------------------------------
combined |      63   -.3257991    .0840035    .6667567   -.4937196   -.1578786
---------+--------------------------------------------------------------------
    diff |             .490624    .2063205                .0780608    .9031873
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.3780
Ho: diff = 0                                     degrees of freedom =       61

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9897         Pr(|T| > |t|) = 0.0206          Pr(T > t) = 0.0103
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    ldl1 |      23    141.9957    10.16953    48.77134    120.9053     163.086
    ldl2 |      23    145.4609    9.745638    46.73844    125.2497    165.6721
---------+--------------------------------------------------------------------
    diff |      23   -3.465217    3.899061    18.69924   -11.55137     4.62094
------------------------------------------------------------------------------
     mean(diff) = mean(ldl1 - ldl9)                               t =  -0.8887
 Ho: mean(diff) = 0                               degrees of freedom =       22

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.1919         Pr(|T| > |t|) = 0.3838          Pr(T > t) = 0.8081

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    ldl1 |      87    138.4667    4.780456    44.58913    128.9634    147.9699
    ldl2 |      87    133.2851    4.487243    41.85422    124.3647    142.2054
---------+--------------------------------------------------------------------
    diff |      87    5.181609    2.541944    23.70967    .1283926    10.23483
------------------------------------------------------------------------------
     mean(diff) = mean(ldl1 - ldl9)                               t =   2.0384
 Ho: mean(diff) = 0                               degrees of freedom =       86

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9777         Pr(|T| > |t|) = 0.0446          Pr(T > t) = 0.0223

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      23    3.465217    3.899061    18.69924    -4.62094    11.55137
  active |      87   -5.181609    2.541944    23.70967   -10.23483   -.1283926
---------+--------------------------------------------------------------------
combined |     110   -3.373637    2.187946    22.94737   -7.710074    .9628011
---------+--------------------------------------------------------------------
    diff |            8.646826    5.340718               -1.939403    19.23305
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   1.6190
Ho: diff = 0                                     degrees of freedom =      108

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9458         Pr(|T| > |t|) = 0.1084          Pr(T > t) = 0.0542
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    ldl1 |      18    142.5667    12.30063    52.18714    116.6146    168.5187
    ldl2 |      18       148.1    12.03566    51.06297     122.707     173.493
---------+--------------------------------------------------------------------
    diff |      18   -5.533332    4.470587    18.96709   -14.96545    3.898781
------------------------------------------------------------------------------
     mean(diff) = mean(ldl1 - ldl9)                               t =  -1.2377
 Ho: mean(diff) = 0                               degrees of freedom =       17

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.1163         Pr(|T| > |t|) = 0.2326          Pr(T > t) = 0.8837

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    ldl1 |      62    142.3452    5.652035    44.50416    131.0432    153.6471
    ldl2 |      62    136.8097    5.194109    40.89846    126.4234    147.1959
---------+--------------------------------------------------------------------
    diff |      62    5.535484    3.210011    25.27566   -.8833302     11.9543
------------------------------------------------------------------------------
     mean(diff) = mean(ldl1 - ldl9)                               t =   1.7244
 Ho: mean(diff) = 0                               degrees of freedom =       61

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9552         Pr(|T| > |t|) = 0.0897          Pr(T > t) = 0.0448

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      18    5.533332    4.470587    18.96709   -3.898781    14.96545
  active |      62   -5.535484    3.210011    25.27566    -11.9543    .8833302
---------+--------------------------------------------------------------------
combined |      80   -3.045001    2.721087    24.33815    -8.46119    2.371188
---------+--------------------------------------------------------------------
    diff |            11.06882    6.437054               -1.746373    23.88401
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   1.7195
Ho: diff = 0                                     degrees of freedom =       78

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9553         Pr(|T| > |t|) = 0.0895          Pr(T > t) = 0.0447
```

STATA Protocol Table 17b

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
  logtg1 |      24    4.777137    .1006159     .492915    4.568998    4.985277
  logtg2 |      24    4.735161    .1095542    .5367036    4.508531    4.961791
---------+--------------------------------------------------------------------
    diff |      24    .0419767    .0804298    .3940241   -.1244051    .2083585
------------------------------------------------------------------------------
     mean(diff) = mean(logtg1 - logtg9)                           t =   0.5219
 Ho: mean(diff) = 0                               degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.6966         Pr(|T| > |t|) = 0.6067          Pr(T > t) = 0.3034

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
  logtg1 |      87     4.88529    .0583837    .5445668    4.769227    5.001353
  logtg2 |      87      4.7163    .0589333    .5496928    4.599144    4.833455
---------+--------------------------------------------------------------------
    diff |      87    .1689901    .0432095    .4030316    .0830924    .2548877
------------------------------------------------------------------------------
     mean(diff) = mean(logtg1 - logtg9)                           t =   3.9109
 Ho: mean(diff) = 0                               degrees of freedom =       86

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9999         Pr(|T| > |t|) = 0.0002          Pr(T > t) = 0.0001

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -.0419767    .0804298    .3940241   -.2083585    .1244051
  active |      87   -.1689901    .0432095    .4030316   -.2548877   -.0830924
---------+--------------------------------------------------------------------
combined |     111   -.1415277    .0382283    .4027597   -.2172872   -.0657683
---------+--------------------------------------------------------------------
    diff |            .1270133    .0924913               -.0563013     .310328
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   1.3732
Ho: diff = 0                                     degrees of freedom =      109

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9138         Pr(|T| > |t|) = 0.1725          Pr(T > t) = 0.0862
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
     tg1 |      24     132.625    12.49635    61.21936    106.7743    158.4757
     tg2 |      24    133.4583     18.8273    92.23457    94.51109    172.4056
---------+--------------------------------------------------------------------
    diff |      24   -.8333333    14.74084    72.21506   -31.32708    29.66041
------------------------------------------------------------------------------
     mean(diff) = mean(tg1 - tg9)                                     t =  -0.0565
 Ho: mean(diff) = 0                               degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.4777         Pr(|T| > |t|) = 0.9554          Pr(T > t) = 0.5223

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
     tg1 |      87    155.2529    11.23634    104.8056    132.9158      177.59
     tg2 |      87    131.5632    9.989244    93.17347    111.7053    151.4212
---------+--------------------------------------------------------------------
    diff |      87    23.68966    8.147814    75.99775    7.492336    39.88697
------------------------------------------------------------------------------
     mean(diff) = mean(tg1 - tg9)                                     t =   2.9075
 Ho: mean(diff) = 0                               degrees of freedom =       86

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9977         Pr(|T| > |t|) = 0.0046          Pr(T > t) = 0.0023

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24    .8333333    14.74084    72.21506   -29.66041    31.32708
  active |      87   -23.68966    8.147814    75.99775   -39.88697   -7.492336
---------+--------------------------------------------------------------------
combined |     111   -18.38739    7.171494    75.55638   -32.59961   -4.175169
---------+--------------------------------------------------------------------
    diff |            24.52299    17.34215               -9.848598    58.89457
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                              t =   1.4141
Ho: diff = 0                                     degrees of freedom =      109

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9199         Pr(|T| > |t|) = 0.1602          Pr(T > t) = 0.0801
```

STATA Protocol For Table 19

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ |   TCH decrease ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        21          2 |        23
           |      18.4        4.6 |      23.0
           |     91.30       8.70 |    100.00
-----------+----------------------+----------
    active |        67         20 |        87
           |      69.6       17.4 |      87.0
           |     77.01      22.99 |    100.00
-----------+----------------------+----------
     Total |        88         22 |       110
           |      88.0       22.0 |     110.0
           |     80.00      20.00 |    100.00

          Pearson chi2(1) =   2.3226   Pr = 0.128
           Fisher's exact =                 0.154
   1-sided Fisher's exact =                 0.105


Logistic regression                               Number of obs   =        110
                                                  LR chi2(1)      =       2.69
                                                  Prob > chi2     =     0.1011
Log likelihood = -53.700057                       Pseudo R2       =     0.0244

------------------------------------------------------------------------------
   oddstch10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   3.134328   2.453089     1.46   0.144     .6760048    14.53246
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | TCH decrease ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        15          2 |        17
           |      13.0        4.0 |      17.0
           |     88.24      11.76 |    100.00
-----------+----------------------+----------
    active |        49         18 |        67
           |      51.0       16.0 |      67.0
           |     73.13      26.87 |    100.00
-----------+----------------------+----------
     Total |        64         20 |        84
           |      64.0       20.0 |      84.0
           |     76.19      23.81 |    100.00

          Pearson chi2(1) =   1.7045   Pr = 0.192
           Fisher's exact =                 0.338
   1-sided Fisher's exact =                 0.162


Logistic regression                               Number of obs   =         84
                                                  LR chi2(1)      =       1.92
                                                  Prob > chi2     =     0.1660
Log likelihood = -45.146099                       Pseudo R2       =     0.0208

------------------------------------------------------------------------------
   oddstch10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   2.755102   2.208606     1.26   0.206      .572504    13.25858
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | HDL increase ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        21          3 |        24
           |      19.0        5.0 |      24.0
           |     87.50      12.50 |    100.00
-----------+----------------------+----------
    active |        67         20 |        87
           |      69.0       18.0 |      87.0
           |     77.01      22.99 |    100.00
-----------+----------------------+----------
     Total |        88         23 |       111
           |      88.0       23.0 |     111.0
           |     79.28      20.72 |    100.00

          Pearson chi2(1) =   1.2597   Pr = 0.262
           Fisher's exact =                 0.395
   1-sided Fisher's exact =                 0.204


Logistic regression                               Number of obs   =        111
                                                  LR chi2(1)      =       1.38
                                                  Prob > chi2     =     0.2406
Log likelihood = -55.947439                       Pseudo R2       =     0.0122

------------------------------------------------------------------------------
   oddshdl10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   2.089552   1.395279     1.10   0.270     .5645094    7.734551
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | HDL increase ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        16          2 |        18
           |      13.5        4.5 |      18.0
           |     88.89      11.11 |    100.00
-----------+----------------------+----------
    active |        44         18 |        62
           |      46.5       15.5 |      62.0
           |     70.97      29.03 |    100.00
-----------+----------------------+----------
     Total |        60         20 |        80
           |      60.0       20.0 |      80.0
           |     75.00      25.00 |    100.00

          Pearson chi2(1) =   2.3895   Pr = 0.122
           Fisher's exact =                 0.214
   1-sided Fisher's exact =                 0.104


Logistic regression                               Number of obs   =         80
                                                  LR chi2(1)      =       2.71
                                                  Prob > chi2     =     0.0995
Log likelihood = -43.630274                       Pseudo R2       =     0.0302

------------------------------------------------------------------------------
   oddshdl10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   3.272727   2.619783     1.48   0.139     .6816042    15.71402
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | TCH/HDL decrease ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        20          3 |        23
           |      16.3        6.7 |      23.0
           |     86.96      13.04 |    100.00
-----------+----------------------+----------
    active |        58         29 |        87
           |      61.7       25.3 |      87.0
           |     66.67      33.33 |    100.00
-----------+----------------------+----------
     Total |        78         32 |       110
           |      78.0       32.0 |     110.0
           |     70.91      29.09 |    100.00

          Pearson chi2(1) =   3.6304   Pr = 0.057
           Fisher's exact =                 0.072
   1-sided Fisher's exact =                 0.045


Logistic regression                               Number of obs   =        110
                                                  LR chi2(1)      =       4.09
                                                  Prob > chi2     =     0.0432
Log likelihood = -64.282617                       Pseudo R2       =     0.0308

------------------------------------------------------------------------------
oddstch/hdl  | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   3.333333    2.19863     1.83   0.068     .9150307    12.14288
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | TCH/HDL decrease ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        11          1 |        12
           |       7.4        4.6 |      12.0
           |     91.67       8.33 |    100.00
-----------+----------------------+----------
    active |        28         23 |        51
           |      31.6       19.4 |      51.0
           |     54.90      45.10 |    100.00
-----------+----------------------+----------
     Total |        39         24 |        63
           |      39.0       24.0 |      63.0
           |     61.90      38.10 |    100.00

          Pearson chi2(1) =   5.5677   Pr = 0.018
           Fisher's exact =                 0.022
   1-sided Fisher's exact =                 0.017


Logistic regression                               Number of obs   =         63
                                                  LR chi2(1)      =       6.64
                                                  Prob > chi2     =     0.0100
Log likelihood = -38.547046                       Pseudo R2       =     0.0793

------------------------------------------------------------------------------
oddstch/hdl  | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   9.035714   9.774044     2.03   0.042     1.084444    75.28661
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ |   LDL decrease ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        18          5 |        23
           |      16.3        6.7 |      23.0
           |     78.26      21.74 |    100.00
-----------+----------------------+----------
    active |        60         27 |        87
           |      61.7       25.3 |      87.0
           |     68.97      31.03 |    100.00
-----------+----------------------+----------
     Total |        78         32 |       110
           |      78.0       32.0 |     110.0
           |     70.91      29.09 |    100.00

          Pearson chi2(1) =   0.7620   Pr = 0.383
           Fisher's exact =                 0.449
   1-sided Fisher's exact =                 0.274


Logistic regression                               Number of obs   =        110
                                                  LR chi2(1)      =       0.80
                                                  Prob > chi2     =     0.3724
Log likelihood = -65.928223                       Pseudo R2       =     0.0060

------------------------------------------------------------------------------
   oddsldl10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |       1.62   .9008996     0.87   0.386      .544694    4.818118
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | LDL decrease ≥10%
       adj |         0          1 |     Total
-----------+----------------------+----------
  inactive |        14          4 |        18
           |      13.1        5.0 |      18.0
           |     77.78      22.22 |    100.00
-----------+----------------------+----------
    active |        44         18 |        62
           |      45.0       17.1 |      62.0
           |     70.97      29.03 |    100.00
-----------+----------------------+----------
     Total |        58         22 |        80
           |      58.0       22.0 |      80.0
           |     72.50      27.50 |    100.00

          Pearson chi2(1) =   0.3245   Pr = 0.569
           Fisher's exact =                 0.766
   1-sided Fisher's exact =                 0.403


Logistic regression                               Number of obs   =         80
                                                  LR chi2(1)      =       0.33
                                                  Prob > chi2     =     0.5627
Log likelihood = -46.886008                       Pseudo R2       =     0.0036

------------------------------------------------------------------------------
   oddsldl10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   1.431818   .9052346     0.57   0.570     .4147009    4.943571
------------------------------------------------------------------------------
```

```
+--------------------+
| Key                |
|--------------------|
|     frequency      |
| expected frequency |
|   row percentage   |
+--------------------+

cflstatus_ | TG decrease ≥10%
           |         0          1 |     Total
-----------+----------------------+----------
  inactive |        13         11 |        24
           |      11.9       12.1 |      24.0
           |     54.17      45.83 |    100.00
-----------+----------------------+----------
    active |        42         45 |        87
           |      43.1       43.9 |      87.0
           |     48.28      51.72 |    100.00
-----------+----------------------+----------
     Total |        55         56 |       111
           |      55.0       56.0 |     111.0
           |     49.55      50.45 |    100.00

          Pearson chi2(1) =   0.2611   Pr = 0.609
           Fisher's exact =                 0.651
   1-sided Fisher's exact =                 0.390


Logistic regression                               Number of obs   =        111
                                                  LR chi2(1)      =       0.26
                                                  Prob > chi2     =     0.6092
Log likelihood = -76.804173                       Pseudo R2       =     0.0017

------------------------------------------------------------------------------
   tg_odds10 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cflstatus    |   1.266234   .5855752     0.51   0.610     .5115312    3.134409
------------------------------------------------------------------------------
```

STATA Protocol Table 20

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      24     136.125    2.493697    12.21657    130.9664    141.2836
   syst2 |      24    135.0833    1.823673    8.934139    131.3108    138.8559
---------+--------------------------------------------------------------------
    diff |      24    1.041667    2.044327    10.01512   -3.187346    5.270679
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =   0.5095
 Ho: mean(diff) = 0                              degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.6924         Pr(|T| > |t|) = 0.6152          Pr(T > t) = 0.3076

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      80     143.325    1.775784     15.8831    139.7904    146.8596
   syst2 |      80      142.05    1.423459     12.7318    139.2167    144.8833
---------+--------------------------------------------------------------------
    diff |      80       1.275    1.278099    11.43166   -1.268992    3.818992
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =   0.9976
 Ho: mean(diff) = 0                              degrees of freedom =       79

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8392         Pr(|T| > |t|) = 0.3215          Pr(T > t) = 0.1608


Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -1.041667    2.044327    10.01512   -5.270679    3.187346
  active |      80      -1.275    1.278099    11.43166   -3.818992    1.268992
---------+--------------------------------------------------------------------
combined |     104   -1.221154    1.085924    11.07429   -3.374827    .9325196
---------+--------------------------------------------------------------------
    diff |            .2333333    2.589902               -4.903724    5.370391
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   0.0901
Ho: diff = 0                                    degrees of freedom =      102

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.5358         Pr(|T| > |t|) = 0.9284          Pr(T > t) = 0.4642
```

```
-> cflstatus16 = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      27    136.9259    2.345467     12.1874    132.1048    141.7471
   syst2 |      27    136.6296    1.900029    9.872838    132.7241    140.5352
---------+--------------------------------------------------------------------
    diff |      27    .2962963    2.084958    10.83376   -3.989397    4.581989
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =   0.1421
 Ho: mean(diff) = 0                               degrees of freedom =       26

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.5560         Pr(|T| > |t|) = 0.8881          Pr(T > t) = 0.4440

-> cflstatus16 = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      77    143.3247    1.831919    16.07502    139.6761    146.9733
   syst2 |      77    141.7792    1.459949      12.811    138.8715     144.687
---------+--------------------------------------------------------------------
    diff |      77    1.545455    1.277406    11.20919   -.9987194    4.089629
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =   1.2098
 Ho: mean(diff) = 0                               degrees of freedom =       76

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8850         Pr(|T| > |t|) = 0.2301          Pr(T > t) = 0.1150

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |      27   -.2962963    2.084958    10.83376   -4.581989    3.989397
       1 |      77   -1.545455    1.277406    11.20919   -4.089629    .9987194
---------+--------------------------------------------------------------------
combined |     104   -1.221154    1.085924    11.07429   -3.374827    .9325196
---------+--------------------------------------------------------------------
    diff |            1.249158    2.485919               -3.681651    6.179967
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   0.5025
Ho: diff = 0                                     degrees of freedom =      102

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.6918         Pr(|T| > |t|) = 0.6164          Pr(T > t) = 0.3082
```

```
-> cflstatus20 = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      46    138.9783    1.915986    12.99485    135.1193    142.8373
   syst2 |      46    139.4348    1.542209    10.45977    136.3286     142.541
---------+--------------------------------------------------------------------
    diff |      46   -.4565217    1.771134    12.01241   -4.023768    3.110725
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =  -0.2578
 Ho: mean(diff) = 0                               degrees of freedom =       45

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.3989         Pr(|T| > |t|) = 0.7978          Pr(T > t) = 0.6011

-> cflstatus20 = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      58    143.7931    2.208541    16.81974    139.3706    148.2156
   syst2 |      58    141.2414    1.784742    13.59219    137.6675    144.8153
---------+--------------------------------------------------------------------
    diff |      58    2.551724     1.33662     10.1794   -.1248114     5.22826
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =   1.9091
 Ho: mean(diff) = 0                               degrees of freedom =       57

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9694         Pr(|T| > |t|) = 0.0613          Pr(T > t) = 0.0306

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       0 |      46    .4565217    1.771134    12.01241   -3.110725    4.023768
       1 |      58   -2.551724     1.33662     10.1794    -5.22826    .1248114
---------+--------------------------------------------------------------------
combined |     104   -1.221154    1.085924    11.07429   -3.374827    .9325196
---------+--------------------------------------------------------------------
    diff |            3.008246    2.176859               -1.309543    7.326035
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   1.3819
Ho: diff = 0                                     degrees of freedom =      102

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9150         Pr(|T| > |t|) = 0.1700          Pr(T > t) = 0.0850
```

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      24    83.29167    1.575951    7.720549    80.03156    86.55177
    dia2 |      24    77.33333    1.695761    8.307496    73.82539    80.84128
---------+--------------------------------------------------------------------
    diff |      24    5.958333    1.802252    8.829196    2.230091    9.686576
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   3.3060
 Ho: mean(diff) = 0                             degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9985         Pr(|T| > |t|) = 0.0031          Pr(T > t) = 0.0015

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      80     82.9875     1.11683    9.989227    80.76451    85.21049
    dia2 |      80      79.575     1.06435    9.519833    77.45647    81.69353
---------+--------------------------------------------------------------------
    diff |      80      3.4125    .9511309    8.507173    1.519321    5.305679
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   3.5878
 Ho: mean(diff) = 0                             degrees of freedom =       79

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9997         Pr(|T| > |t|) = 0.0006          Pr(T > t) = 0.0003

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      24   -5.958333    1.802252    8.829196   -9.686576   -2.230091
  active |      80     -3.4125    .9511309    8.507173   -5.305679   -1.519321
---------+--------------------------------------------------------------------
combined |     104          -4      .84397    8.606839   -5.673815   -2.326185
---------+--------------------------------------------------------------------
    diff |           -2.545833    1.997082               -6.507036     1.41537
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =  -1.2748
Ho: diff = 0                                    degrees of freedom =      102

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.1026         Pr(|T| > |t|) = 0.2053          Pr(T > t) = 0.8974
```

```
-> cflstatus16 = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      27     83.7037    1.442946    7.497768    80.73769    86.66972
    dia2 |      27    78.44444    1.761679    9.153954    74.82326    82.06563
---------+--------------------------------------------------------------------
    diff |      27    5.259259    1.740741    9.045154    1.681115    8.837403
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   3.0213
 Ho: mean(diff) = 0                             degrees of freedom =       26

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9972         Pr(|T| > |t|) = 0.0056          Pr(T > t) = 0.0028

-> cflstatus16 = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      77    82.83117    1.152934    10.11695     80.5349    85.12744
    dia2 |      77    79.27273    1.065785    9.352225    77.15003    81.39542
---------+--------------------------------------------------------------------
    diff |      77    3.558442    .9645978    8.464311    1.637279    5.479605
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   3.6890
 Ho: mean(diff) = 0                             degrees of freedom =       76

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9998         Pr(|T| > |t|) = 0.0004          Pr(T > t) = 0.0002

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      27   -5.259259    1.740741    9.045154   -8.837403   -1.681115
  active |      77   -3.558442    .9645978    8.464311   -5.479605   -1.637279
---------+--------------------------------------------------------------------
combined |     104          -4      .84397    8.606839   -5.673815   -2.326185
---------+--------------------------------------------------------------------
    diff |           -1.700818    1.927079               -5.52317    2.121535
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =  -0.8826
Ho: diff = 0                                   degrees of freedom =      102

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.1898         Pr(|T| > |t|) = 0.3795          Pr(T > t) = 0.8102
```

```
-> cflstatus20 = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      46    81.34783     1.50401    10.20069    78.31859    84.37706
    dia2 |      46     78.3913    1.492486    10.12253    75.38528    81.39733
---------+--------------------------------------------------------------------
    diff |      46    2.956522    1.375759    9.330849    .1856018    5.727442
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   2.1490
 Ho: mean(diff) = 0                             degrees of freedom =       45

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9815         Pr(|T| > |t|) = 0.0370          Pr(T > t) = 0.0185

-> cflstatus20 = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      58    84.41379    1.144712    8.717867    82.12155    86.70604
    dia2 |      58    79.58621    1.126063    8.575842     77.3313    81.84111
---------+--------------------------------------------------------------------
    diff |      58    4.827586    1.046741    7.971744    2.731523    6.923649
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   4.6120
 Ho: mean(diff) = 0                             degrees of freedom =       57

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      46   -2.956522    1.375759    9.330849   -5.727442   -.1856018
  active |      58   -4.827586    1.046741    7.971744   -6.923649   -2.731523
---------+--------------------------------------------------------------------
combined |     104          -4      .84397    8.606839   -5.673815   -2.326185
---------+--------------------------------------------------------------------
    diff |            1.871064     1.69752               -1.495958    5.238086
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   1.1022
Ho: diff = 0                                   degrees of freedom =      102

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.8635         Pr(|T| > |t|) = 0.2730          Pr(T > t) = 0.1365
```

STATA Protocol Table 21

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      16    147.4375    2.983243    11.93297    141.0789    153.7961
   syst2 |      16    148.6875    2.861699     11.4468    142.5879    154.7871
---------+--------------------------------------------------------------------
    diff |      16       -1.25     3.02283    12.09132   -7.693009    5.193009
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =  -0.4135
 Ho: mean(diff) = 0                              degrees of freedom =       15

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.3425         Pr(|T| > |t|) = 0.6851          Pr(T > t) = 0.6575

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   syst1 |      52    147.1923    1.560262    11.25121      144.06    150.3247
   syst2 |      52    142.8269    1.316653    9.494521    140.1836    145.4702
---------+--------------------------------------------------------------------
    diff |      52    4.365385    1.435656    10.35266    1.483185    7.247584
------------------------------------------------------------------------------
     mean(diff) = mean(syst1 - syst9)                             t =   3.0407
 Ho: mean(diff) = 0                              degrees of freedom =       51

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9981         Pr(|T| > |t|) = 0.0037          Pr(T > t) = 0.0019

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      16        1.25     3.02283    12.09132   -5.193009    7.693009
  active |      52   -4.365385    1.435656    10.35266   -7.247584   -1.483185
---------+--------------------------------------------------------------------
combined |      68   -3.044118    1.328824    10.95777   -5.696462    -.391773
---------+--------------------------------------------------------------------
    diff |            5.615385    3.079701               -.533436    11.76421
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   1.8234
Ho: diff = 0                                    degrees of freedom =       66

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9636         Pr(|T| > |t|) = 0.0728          Pr(T > t) = 0.0364
```

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      13    90.15385    .7666624    2.764241    88.48343    91.82426
    dia2 |      13    86.76923    1.687639     6.08487    83.09218    90.44628
---------+--------------------------------------------------------------------
    diff |      13    3.384615    1.752429    6.318471   -.4335985    7.202829
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   1.9314
 Ho: mean(diff) = 0                        degrees of freedom =       12

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9613         Pr(|T| > |t|) = 0.0774          Pr(T > t) = 0.0387

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
    dia1 |      21    93.33333    1.051831    4.820097    91.13925    95.52742
    dia2 |      21     82.7619    2.542875    11.65292    77.45756    88.06625
---------+--------------------------------------------------------------------
    diff |      21    10.57143    2.378046    10.89758    5.610912    15.53195
------------------------------------------------------------------------------
     mean(diff) = mean(dia1 - dia9)                               t =   4.4454
 Ho: mean(diff) = 0                        degrees of freedom =       20

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9999         Pr(|T| > |t|) = 0.0002          Pr(T > t) = 0.0001

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      13   -3.384615    1.752429    6.318471   -7.202829    .4335985
  active |      21   -10.57143    2.378046    10.89758   -15.53195   -5.610912
---------+--------------------------------------------------------------------
combined |      34   -7.823529    1.706896     9.95283   -11.29624   -4.350823
---------+--------------------------------------------------------------------
    diff |            7.186813    3.332935                .3978466    13.97578
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   2.1563
Ho: diff = 0                              degrees of freedom =       32

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9807         Pr(|T| > |t|) = 0.0387          Pr(T > t) = 0.0193
```

STATA Protocol For Table 22a

```
-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
procam~1 |      15    5.729833    1.338338    5.183362    2.859382    8.600283
procam~2 |      15    6.500762    1.402058    5.430148    3.493646    9.507877
---------+--------------------------------------------------------------------
    diff |      15   -.7709293    .5056975    1.958558   -1.855542    .3136839
------------------------------------------------------------------------------
     mean(diff) = mean(procam_risk1 - procam_risk9)               t =  -1.5245
 Ho: mean(diff) = 0                               degrees of freedom =       14

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0748         Pr(|T| > |t|) = 0.1497          Pr(T > t) = 0.9252

-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
procam~1 |      56    6.800217    .7178748    5.372083    5.361564    8.238871
procam~2 |      56    5.506427     .635204    4.753432     4.23345    6.779405
---------+--------------------------------------------------------------------
    diff |      56     1.29379    .4270802    3.195976    .4379021    2.149678
------------------------------------------------------------------------------
     mean(diff) = mean(procam_risk1 - procam_risk9)               t =   3.0294
 Ho: mean(diff) = 0                               degrees of freedom =       55

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9981         Pr(|T| > |t|) = 0.0037          Pr(T > t) = 0.0019

-> cflstatus_adj = inactive
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
logpro~1 |      15    1.473493     .186121    .7208436    1.074303    1.872683
logpro~2 |      15    1.555692    .2196713    .8507835    1.084544    2.026841
---------+--------------------------------------------------------------------
    diff |      15   -.0821996    .0952766    .3690045   -.2865475    .1221483
------------------------------------------------------------------------------
     mean(diff) = mean(logprocam1 - logprocam9)                   t =  -0.8627
 Ho: mean(diff) = 0                               degrees of freedom =       14

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.2014         Pr(|T| > |t|) = 0.4028          Pr(T > t) = 0.7986
```

```
-> cflstatus_adj = active
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
logpro~1 |      56    1.657313    .0977249    .7313061    1.461468    1.853158
logpro~2 |      56    1.419398    .1010052    .7558537    1.216979    1.621817
---------+--------------------------------------------------------------------
    diff |      56     .237915    .0581929    .4354761    .1212938    .3545363
------------------------------------------------------------------------------
     mean(diff) = mean(logprocam1 - logprocam9)                    t =   4.0884
 Ho: mean(diff) = 0                                degrees of freedom =       55

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9999         Pr(|T| > |t|) = 0.0001          Pr(T > t) = 0.0001

Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      15    .0821996    .0952766    .3690045   -.1221483    .2865475
  active |      56    -.237915    .0581929    .4354761   -.3545363   -.1212938
---------+--------------------------------------------------------------------
combined |      71   -.1702852    .0522123    .4399485   -.2744193   -.0661511
---------+--------------------------------------------------------------------
    diff |            .3201146    .1116425                .0904069    .5498223
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.8673
Ho: diff = 0                     Satterthwaite's degrees of freedom =  25.4908

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9959         Pr(|T| > |t|) = 0.0082          Pr(T > t) = 0.0041
```

STATA Protocol For Table 22b

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      15    16.64974    13.80337    53.46024   -12.95555    46.25503
  active |      56   -14.69046    4.086486    30.58046   -22.87996   -6.500959
---------+--------------------------------------------------------------------
combined |      71   -8.069291     4.55387    38.37159    -17.1517    1.013116
---------+--------------------------------------------------------------------
    diff |              31.3402    10.58394                10.22582    52.45459
------------------------------------------------------------------------------
    diff = mean(inactive) - mean(active)                          t =   2.9611
Ho: diff = 0                                     degrees of freedom =       69

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9979         Pr(|T| > |t|) = 0.0042          Pr(T > t) = 0.0021

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      18     13.0761    11.84238    50.24297   -11.90914    38.06134
  active |      53   -15.25074    4.232484    30.81295   -23.74385   -6.757643
---------+--------------------------------------------------------------------
combined |      71   -8.069291     4.55387    38.37159    -17.1517    1.013116
---------+--------------------------------------------------------------------
    diff |             28.32684      9.9769                8.423474    48.23021
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   2.8392
Ho: diff = 0                                     degrees of freedom =       69

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9970         Pr(|T| > |t|) = 0.0059          Pr(T > t) = 0.0030

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
inactive |      30    8.055295    7.993236    43.78076   -8.292709     24.4033
  active |      41   -19.86777    4.551413    29.14326   -29.06652   -10.66902
---------+--------------------------------------------------------------------
combined |      71   -8.069291     4.55387    38.37159    -17.1517    1.013116
---------+--------------------------------------------------------------------
    diff |             27.92306    8.655793                10.65523     45.1909
------------------------------------------------------------------------------
    diff = mean(0) - mean(1)                                      t =   3.2259
Ho: diff = 0                                     degrees of freedom =       69

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9990         Pr(|T| > |t|) = 0.0019          Pr(T > t) = 0.0010
```

APPENDIX 2: DESCRIPTION OF THE ELECTRONIC LIFESTYLE FILE (ELF)

APPENDIX 3: ETHICS APPROVAL & PARTICIPANT FORMS

LANDESÄRZTEKAMMER BADEN-WÜRTTEMBERG
KÖRPERSCHAFT DES ÖFFENTLICHEN RECHTS
ETHIK-KOMMISSION

Landesärztekammer Baden-Württemberg • Postfach 760561 • 70573 Stuttgart

Vorab per Fax 0721 1615528

adiphea GmbH
Gesundheitslabor
Herrn Lutz E. Kraushaar
Östliche Rheinbrückenstr. 50
76187 Karlsruhe

10.02.2009

Durchwahl: -55
Fax: 856
Unser Zeichen: ag
Aktenzeichen: **2008-100-f**

Verbesserung der Effizienz von Verhaltensänderungsinterventionen für die Prävention kardiometaboler Erkrankungen
(Prüfplan rev. vom 14.10.08; Teilnehmerinformation und Einverständniserklärung undatiert mit Schreiben vom 14.10.08)

Sehr geehrter Herr Kraushaar,

die Studie hat der Ethik-Kommission in ihren Sitzungen am 07.10.08, am 28.10.08 und am 03.02.09 erneut zur berufsrechtlichen Beratung vorgelegen.

Nach Abwägung der ethischen und rechtlichen Probleme ist die Ethikkommission zu einer zustimmenden Beurteilung gekommen. Sie empfiehlt aber folgende Änderungen und Ergänzungen:

1. In der Patientenaufklärung sollten keine medizinischen Fachausdrücke verwendet werden oder sie sollten erklärt werden. Die Patienteninformation sollte in laienverständlicher Sprache abgefasst werden.
2. Die Angaben zum Datenschutz in der Patienteninformation und Einverständniserklärung sind unzureichend. Wir bitten um Verwendung der beigefügten Mustertexte (Anlage).
3. Bei akuten Erkrankungen (z. B. Infekten) sollte das Bewegungsprogramm unterbrochen werden.
4. Zur adiphea GmbH werden weiterhin keine Informationen geliefert.

Mit freundlichen Grüßen

Dr. med. G. Hook
Vorsitzender der Ethik-Kommission

Anlage: Teilnehmerliste der Sitzung
Mustertexte

Jahnstraße 40 • 70597 Stuttgart • U5 U8 (Degerloch)
Telefon 0711-76989-0 • Telefax 0711-76989-50
Internet www.aerztekammer-bw.de/ethik

Baden-Württembergische Bank AG, Tübingen • (BLZ 641 200 30) 1 208 607 701
Deutsche Apotheker- und Ärztebank Stuttgart • (BLZ 300 606 01) 000 1678 809
Postbank Stuttgart • (BLZ 600 100 70) 164 04-703

PROBANDEN INFORMATION

Verbesserung der Effizienz und Adhärenz in Verhaltensänderungsinterventionen für die Prävention chronischer lebensstilbedingter kardiometaboler Erkrankungen.

Probanden-Information

Liebe Studienteilnehmerin, lieber Studienteilnehmer

Freundlicherweise haben Sie sich bereit erklärt, an diesem Interventionsprojekt teilzunehmen, das die Universität Bielefeld in Kooperation mit der Siemens Betriebskrankenkasse, der Siemens AG Karlsruhe und der adiphea GmbH durchführt. Das Projekt beschäftigt sich mit der Verhütung der Herz-Kreislauferkrankungen durch individualisierte Bewegungsprogramme. Ziel der Intervention ist es, (a) ein auf Ihr Risikoprofil zugeschnittenes Bewegungsverhalten in ein stabiles Gewohnheitsverhalten zu überführen, um damit (b) Ihr Risiko für die lebensstilbedingten Herz-Kreislauferkrankungen und den Diabetes Mellitus Typ 2 nachhaltig zu verringern. Neu an dieser Intervention ist die Kombination aus ärztlicher Betreuung und einer internetbasierten Anwendung zur Motivation und für die Adhärenz- und Fortschrittskontrolle.

Hintergrund

Wissenschaftliche Studien belegen einen ursächlichen Zusammenhang zwischen Bewegungsmangel und chronischen Erkrankungen des Herz-Kreislaufsystems (z.B. Atherosklerose, Bluthochdruck, Herzinfarkt, Schlaganfall) und des Stoffwechsels (Insulinresistenz, Diabetes).

Wissenschaftliche Studien bestätigen auch, dass die Aufnahme von Ausdauer- und Kraftsport das Risiko für diese Krankheiten bei bislang bewegungsarmen Menschen signifikant reduzieren kann. Deshalb haben medizinische Gesellschaften und Gesundheits-organisationen, wie beispielsweise die American Heart Association (AHA), das American College of Sports Medicine (ACSM), das Institute of Medicine (IOM) und die Weltgesundheitsbehörde (WHO), Konsensusempfehlungen für ein risikoreduzierendes Mindestmass an Ausdauersport formuliert. Trotz dieser mittlerweile zum Allgemeinwissen gewordenen Erkenntnisse fällt es den meisten Menschen schwer, mehr Bewegung in ihr Leben zu bringen. Somit erreichen weniger als 20% der erwachsenen Deutschen das empfohlene Minimum von 150 Minuten moderater bis intensiver Bewegung pro Woche.

Damit das angestrebte Mehr an Bewegung wirksam und nachhaltig in die persönlichen Lebensroutinen eingebaut werden kann, muss es sowohl auf das individuelle Risikoprofil des Einzelnen zugeschnitten werden, als auch auf dessen Fähigkeiten, Neigungen und Lebenswelt. Der dafür notwendige Aufwand übersteigt meist die dem betreuenden Arzt zur Verfügung stehenden Resourcen. Demgegenüber bieten Internet-basierte Programme die Möglichkeit der Individualisierung, ihnen fehlt aber die notwendige medizinische Betreuung.

In der Primärprävention der chronischen lebensstilbedingten Erkrankungen wird bislang keine Kombination dieser beiden Strategien angeboten.

In diesem Projekt möchten wir eine in die ärztliche Praxis eingebundene internetbasierte telemetrische Anwendung erproben. Ziel ist es, klinische Betreuung und Individualisierung teilnehmer- und praxisgerecht so zu verknüpfen, dass das auf das individuelle Teilnehmerprofil zugeschnittene Bewegungsprogramm zu einer effizienten, nachhaltigen und signifikanten Reduzierung des Krankheitsrisikos führt.

Nutzen und Risiken der Teilnahme

Ihr Nutzen: Sie erhalten die Möglichkeit durch die Teilnahme an einem auf Ihr persönliches Gesundheitsprofil zugeschnittenen Bewegungsprogramm, Ihr Risiko für die lebensstilbedingten chronischen Herz-Kreislauferkrankungen und den Diabetes Mellitus zu verringern.

Ihr Risiko: Bewegung ungewohnter und höherer Intensität birgt ein Verletzungsrisiko des Bewegungsapparats, beispielsweise der Bänder, Sehnen, Gelenke und Muskeln. In Abhängigkeit von Trainingszustand und Trainingsintensität besteht beim Neu- oder Wiedereinsteiger in ein aktiveres Leben ein Risiko für kardiale Zwischenfälle, z. B. Herzinfarkt oder plötzlicher Herztod.

Allerdings reduziert ein aktiver Lebensstil diese Risiken so substantiell und nachhaltig, dass der zu erwartende Nutzen das tatsächliche Risiko, das mit der Aufnahme eines aktiveren Lebensstils zunächst verbunden ist, deutlich übersteigt.

Bei der Blutentnahme bestehen Risiken für Infektion, Hämatom, Blutverlust. Diese Risiken können aber bei sach- und leitliniengerechter Durchführung weitgehend ausgeschlossen werden.

Durchführung der Projekts:

Untersuchungen

Vor dem Beginn der Intervention und nach Abschluss der 6-monatigen Interventionsperiode werden folgende Messungen durchgeführt:

- Ermittlung der Körperzusammensetzung durch Bioimpedanzanalyse
- Ermittlung des Bewegungsverhaltens
- Ermittlung Ihres Gesundheitszustandes mittels Blutentnahme aus der Armvene
- Messung Ihres Blutdrucks

Messung der Körperzusammensetzung

Bei der phasensensitiven multifrequenten Bioimpedanzanalyse wird über 4 Hautelektroden an Fuss und Hand ein homogenes elektrisches Wechselstromfeld mit konstanter Stromstärke erzeugt und anschließend der Gesamtwiderstand des Körpers gemessen. Mit dieser ungefährlichen, schmerzfreien und genauen Methode lässt sich der Körperwassergehalt bestimmen und daraus der Fettgehalt des Körpers ableiten. Zusätzlich wird Ihr Körpergewicht und Ihre Körpergröße gemessen.

Ermittlung des Bewegungsverhaltens

Zur Ermittlung des Bewegungsverhaltens tragen Sie für 48 Stunden einen leichten (82 Gramm) und unauffälligen Armbandsensor über dem Trizepsmuskel des dominanten Oberarms. Die im Armband eingebauten Beschleunigungsmesser, Hauttemperatur- und Hautwiderstandssensoren nehmen im Minutentakt Messwerte auf und speichern diese im Datenspeicher des Armbands. Nach Abschluss der Tragezeit werden diese Daten auf einem PC ausgewertet. Sie geben Aufschluss über das Bewegungsverhalten, das in Metabolischen Äquivalenten und geleisteten Schritten dargestellt wird.

Blutentnahme

Eine Nüchtern-Blutentnahme aus Ihrer Vene (ca. 20 ml) dient zur Bestimmung des Blutzuckers, der Cholesterinfraktionen, der Triglyzeride, des CRP und der Bestimmung eines kleinen Blutbildes.

Messung des Blutdrucks

Ihr Blutdruck wird liegend an beiden Oberarmen mit einem oszillometrischen automatischen Messverfahren gemessen.

Intervention

Basierend auf den Ergebnissen der Eingangsuntersuchung erstellen wir in der Ergebnisbesprechung gemeinsam mit Ihnen einen Bewegungsplan, der aus Ausdauer- und/oder Krafttrainingskomponenten bestehen wird. Ziel der gemeinsamen Ausarbeitung des Trainingsplans ist es, Ihren Trainingsplan auf Ihr Gesundheitsprofil sowie auf Ihre Fähigkeiten, Neigungen und Ihre Lebenswelt anzupassen. Dem gemeinsam verabschiedeten Plan legen wir ein Punktesystem zugrunde, das es Ihnen ermöglicht, Ihr abgeleistetes Bewegungsvolumen jeweils mit einer Anzahl von Punkten zu bewerten. Durch regelmässige Eingabe in eine Internet-basierte telemetrische Anwendung können Sie und wir Ihren Fortschritt im Soll-Ist Vergleich erkennen. In diese telemetrische Anwendung können Sie auch Ihr Körpergewicht, sowie gegebenenfalls zu Hause gemessene Werte für Blutdruck und Blutzucker eingeben. Bei Abweichungen von den Sollwerten des Trainingsplans kontaktieren wir Sie um Ihnen bei der Lösung eventueller Probleme mit der Umsetzung des Plans zu helfen.

Ablauf

Phase 1 **Eingangsuntersuchung**

Termin 1: Nüchtern-Blutentnahme (durch betriebsärztliche Dienststelle oder Ihren Hausarzt)

Termin 2: Bestimmung von Körperzusammensetzung, -größe, Gewicht Bauchumfang und Blutdruck, sowie Anlegen des Armbandsensors (adiphea Gesundheitslabor)

Termin 3: Rückgabe des Armbandsensors (adiphea Gesundheitslabor)

Termin 4: Ergebnisbesprechung und Erstellung des Trainingsplans (adiphea Gesundheitslabor)

Phase 2 **Interventionsphase: Umsetzung des Trainingsplans mit telemetrischer Fortschrittserfassung und -kontrolle**

Phase 3 **Abschlussuntersuchung, Ergebnisauswertung und -besprechung**

Termin 1: Nüchtern-Blutentnahme (durch betriebsärztliche Dienststelle oder Ihren Hausarzt)

Termin 2: Bestimmung von Körperzusammensetzung, -größe, Gewicht Bauchumfang und Blutdruck, sowie Anlegen des Armbandsensors (adiphea Gesundheitslabor)

Termin 3: Rückgabe des Armbandsensors (adiphea Gesundheitslabor)

Termin 4: Ergebnisbesprechung und weiterführende Empfehlung (adiphea Gesundheitslabor)

Die Termine für Phase 1 und Phase 3 sollten jeweils innerhalb von 7-10 Tagen durchgeführt werden.

Freiwilligkeit der Teilnahme

Ihre Teilnahme an diesem Projekt ist freiwillig und kann jederzeit ohne Angabe von Gründen abgebrochen werden. Im Falle eines Rücktritts wird bereits gewonnenes Datenmaterial vernichtet, sofern Sie das wünschen.

Datenschutz und Vertraulichkeit

Die Vorschriften über die ärztliche Schweigepflicht und den Datenschutz werden eingehalten. Es werden gegebenenfalls nur anonymisierte Datenbögen ohne Namensnennung weitergegeben. Die Internet-basierte Anwendung ist nur über Passwort und Benutzername zugänglich und wird auf einem dezidierten Server verschlüsselungszertifiziert zugangsgesichert. Personenbezogene Daten verbleiben bei der Projektleitung des adiphea Gesundheitslabors und werden nach Abschluss des Projekts 10 Jahre aufbewahrt (gemäß den Regeln zur „Sicherung guter wissenschaftlicher Praxis“ der deutschen Forschungsgemeinschaft).

Wir bedanken uns für Ihre Teilnahme und Kooperation.

DECLARATION INFORMED CONSENT

Einverständniserklärung

Name: _____

Geburtsdatum: _____

Das Original dieser Einwilligungserklärung verbleibt bei den Unterlagen. Eine Kopie der Einwilligungserklärung wird dem Patienten ausgehändigt.

Ich _____

(Vorname, Name)

erkläre, dass ich die Probanden/Patienteninformation zur wissenschaftlichen Untersuchung:

„ Verbesserung der Effizienz und Adhärenz in Verhaltensänderungsinterventionen für die Prävention chronischer lebensstilbedingter kardiometaboler Erkrankungen. “

und diese Einwilligungserklärung erhalten habe.

- Ich wurde für mich ausreichend mündlich und schriftlich über die wissenschaftliche Untersuchung informiert.
- Ich erkläre, dass ich damit einverstanden bin, dass Blut, Urin und/oder Gewebe, welches entnommen wird und nicht für die Routineuntersuchung nötig ist, für die o. g. wissenschaftliche Untersuchung genutzt werden kann.
- Ich weiss, dass ich jederzeit meine Einwilligung ohne Angaben von Gründen, widerrufen kann, ohne dass dies für mich nachteilige Folgen hat.
- **Ich bin damit einverstanden, dass die im Rahmen der wissenschaftlichen Untersuchung über mich erhobenen Krankheitsdaten sowie meine sonstigen mit dieser Untersuchung zusammenhängenden personenbezogenen Daten aufgezeichnet werden. Es wird gewährleistet, dass meine personenbezogenen Daten nicht an Dritte weitergegeben werden. Bei der Veröffentlichung in einer wissenschaftlichen Zeitung wird aus den Daten nicht hervorgehen, wer an dieser Untersuchung teilgenommen hat. Meine persönlichen Daten unterliegen dem Datenschutzgesetz.**

Mit der vorstehend geschilderten Vorgehensweise bin ich einverstanden und bestätige dies mit meiner Unterschrift.

_____	den, _____	_____
(Ort)	(Datum)	(Teilnehmer)
_____	den, _____	_____
(Ort)	(Datum)	(Projektleiter)
		_____
		(Name des Projektleiters)

HEALTH HISTORY QUESTIONNAIRE

Eingangsfragebogen zur Teilnahme an einer Bewegungsintervention

Ich garantiere die ehrliche Beantwortung der folgenden Fragen. *adiphea* garantiert die vertrauliche Behandlung meiner Angaben.

Leiden Sie an folgenden Krankheiten, bzw. haben Sie folgende Krankheiten schon einmal gehabt?

Ja	Nein	
☐	☐	Herzerkrankung
☐	☐	Operation am Herzen: Katheterisierung, Angioplastie, Herzschrittmacher, Herzverpflanzung
☐	☐	Schlaganfall oder TIA
☐	☐	Bluthochdruck (>140 mmHg systolisch und/oder >90 mmHg diastolisch) oder nehmen Sie verschreibungspflichtige Blutdruckmedikamente?
☐	☐	Diabetes: wenn ja bitte ankreuzen ob Typ 1 ☐ oder Typ 2 ☐
☐	☐	Asthma oder nehmen Sie Medikamente für Asthma?
☐	☐	Andere Lungenerkrankung
☐	☐	Andere Erkrankung die Sie von der Teilnahme an einem Bewegungsprogramm abhält (Krebs, Osteoporose, Arthrose, Erkrankung von Leber, Niere, Schilddrüse)
☐	☐	Sind Sie schwanger oder haben Sie Grund zur Annahme schwanger zu sein?

Leiden Sie an folgenden Zeichen oder Symptomen oder sind diese jemals bei Ihnen aufgetreten?

Ja	**Nein**	
☐	☐	Schwindel, Ohnmacht, Bewusstlosigkeit, Luftnot
☐	☐	Schmerzen am Herzen oder im Brustbereich
☐	☐	Herzstolpern, Herzaussetzer, Herzrasen
☐	☐	Wurden bei Ihnen Herzgeräusche diagnostiziert?
☐	☐	Nächtliche Anfälle von Atemnot oder Kurzatmigkeit
☐	☐	Schwellungen oder Wasseransammlungen im Bereich der Fussgelenke
☐	☐	Gehschmerzen oder Missempfindungen in den Beinen nach kurzem Gehen
☐	☐	Erkrankungen oder Behinderungen des Bewegungsapparates

Bestehen bei Ihnen folgende Risikofaktoren?

Ja	**Nein**	
☐	☐	Sie rauchen oder haben mit dem Rauchen innerhalb der letzten 6 Monate aufgehört
☐	☐	Erkrankung (Herzkrankheit, Herzinfarkt, Schlaganfall, Herzoperation, Herzschrittmacher) oder plötzlicher Tod des Vaters oder Bruders vor dem 55. Lebensjahr, oder der Mutter oder Schwester vor dem 65. Lebensjahr?
☐	☐	Alkohol- oder Medikamentenmissbrauch

Datum	**Name**	**Unterschrift**