Physical Activity Without Weight Loss Reduces the Development of Cardiovascular Disease Risk Factors– A Prospective Cohort Study of More Than One Hundred Thousand Adults

Short title**: Physical activity, Obesity and Cardiovascular Health**

David Martinez-Gomez PhD[1,2], Carl J Lavie MD[3], Mark Hamer PhD[4], Veronica Cabanas-Sanchez PhD[2], Esther Garcia-Esquinas PhD[1], Helios Pareja-Galeano[5], Ellen Struijk PhD[1], Kabir P Sadarangani MSc[6,7], Francisco B Ortega PhD[8], Fernando Rodríguez-Artalejo MD PhD[1,2].

[1]Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid/ IdiPaz, CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain. [2]IMDEA Food Institute. CEI UAM+CSIC, Madrid, Spain. [3]Department of Cardiovascular Disease, John Ochsner Heart & Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, USA. [4]Institute of Sport Exercise & Health, Division of Surgery & Interventional Science, Faculty of Medical Sciences, University College London, London, UK. [5]Faculty of Sport Sciences, Universidad Europea de Madrid, Spain. [6]School of Physiotherapy, Faculty of Health Sciences, Universidad San Sebastián, Lota, Santiago, Chile. [7]Escuela de Kinesiología, Facultad de Salud y Odontología, Universidad Diego Portales, Santiago, Chile. [8]PROFITH "PROmoting FITness and Health through physical activity" research group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Spain; Department of Biosciences and Nutrition at NOVUM, Karolinska Institutet, Huddinge, Sweden.

Corresponding author: David Martinez-Gomez. d.martinez@uam.es

Word count: 3066 words.

Abstract

Purpose: Whether physical activity (PA) might have certain benefits for cardiovascular disease (CVD) primordial prevention even in the absence of clinically significant weight loss is of public health interest. In this study, we examined the independent and combined associations of simultaneous changes in PA and body weight with the subsequent development of major CVD risk factors in adults.

Methods: This prospective analysis included 116,134 healthy men and women, aged ≥18 years, with at least 3 medical examinations from the Taiwan MJ Cohort. Two-year changes in PA and body weight between the first and second examination were linked to subsequent development of hypertension, hypercholesterolemia, atherogenic dyslipidemia, metabolic syndrome, type 2 diabetes mellitus (T2DM), and chronic inflammation, which were assessed by physical examinations and laboratory tests.

Results: During an average follow-up of 5.7±4.1 years after the second examination, 10840 individuals developed hypertension, 10888 hypercholesterolemia, 6078 atherogenic dyslipidemia, 13223 metabolic syndrome, 4816 T2DM, and 2027 inflammation. Weight gain was associated with a subsequent higher risk of all CVD risk factors, with HR (95%CI) ranging from 1.11 (1.00-1.23) for inflammation to 1.74 (1.67-1.82) for metabolic syndrome, compared with participants who lost weight. A stable weight was also associated with a higher risk of all CVD risk factors except with inflammation. In combined analyses, participants who simultaneously gained weight and decreased PA levels had the highest risk compared with those who lost weight and increased PA. Increasing or maintaining PA reduced the increased subsequent risk of some CVD risk factors among participants who maintained a stable weight or gained weight. Among participants who lost weight, decreased PA was not associated with an increased risk.

Conclusions: Although weight loss is crucial for the prevention of CVD risk factors, increasing or maintaining PA is also important to prevent them among adults who gain or maintain their weight.

Keywords: physical activity, weight loss, obesity, cardiovascular disease risk factors, prevention, prospective.

Abbreviations and acronyms: BF%, body fat percentage; BMI, Body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HDL-C, High-density lipoprotein cholesterol; HR, hazard ratios; MET, metabolic equivalent of task; PA, physical activity; T2DM, type 2 diabetes mellitus.

Conflicts of interest: There are no conflicts of interest relating to this manuscript.

Introduction

Cardiovascular disease (CVD) remains one of the main causes of death globally, and the major CVD risk factors are hypertension, hypercholesterolemia, atherogenic dyslipidemia, the metabolic syndrome, type 2 diabetes mellitus (T2DM) and chronic inflammation [1-3]. Primordial prevention consists of delaying the development of these CVD risk factors, and has been acknowledged as an important population-wide approach for preventing the onset and progression of CVD [4,5].

Excess body weight or fat is strongly associated with increased incidence of major CVD risk factors, as well as CVD morbidity and mortality [6,7]. A healthy weight is, therefore, one of the main tools for CVD prevention [7]. Regular physical activity (PA) is also crucial for CVD prevention because it has been consistently associated with lower incidence of CVD risk factors as well as fatal and non-fatal CVD events [8-10].

One of the cardioprotective effects of regular PA has been attributed to increased total energy expenditure resulting in negative energy balance and, consequently, weight control [8-12]. However, recent small clinical trials suggest that PA and exercise training might have certain benefits on some major CVD risk factors even in the absence of clinically significant weight or fat loss [12]. To date, it is unknown whether this evidence may also apply to the general population because previous cohort studies on the potential effect of PA on CVD risk factors regardless of body weight were mostly based on single baseline assessments [9,13]. Since weight and PA change over time, and the patterns of change vary among individuals, the purpose of this study was to examine the independent and combined associations of simultaneous changes in PA and body weight or fat with the subsequent development of major CVD risk factors in a large cohort of healthy adults.

Material and methods

Participants

This work was conducted using the Taiwan MJ Cohort resource [14,15], an ongoing and dynamic prospective study of apparently healthy people of all ages who participate in a large health screening service by the MJ Group, Taiwan (www.mjclinic.com.tw). The MJ Cohort has enrolled around 600,000 individuals since 1994. Participants completed a standardized protocol including a survey, physical examinations, and laboratory tests in the MJ Health Screening Center during a morning, which conformed to ISO 9001 for quality management. After the first examination, all participants were encouraged to return every year, and all data are updated by the MJ Health Research Foundation.

For the current study, we selected men and women aged ≥18 years who attended the first examination (baseline) during 1997-2016. The exclusion criteria were: (i) history of cancer or CVD at the first and/or second examinations, (ii) having less than three examinations through 2016 with valid data on the specific CVD risk factors, (iii) lacking data at the first and second examinations on body weight and PA, (iv) incomplete data at the first examination on main covariates, and (v) prevalence or incidence of the specific CVD risk factor at the first and/or second examinations. Accordingly, a total of 116,134 individuals with the first examination between 1997 and 2013 formed the analytical sample for this work; specifically, we used data on n=97,416 for the analyses on the incidence of hypertension, n=98,837 for hypercholesterolemia, n=93,707 for atherogenic dyslipidemia, n=93,066 for metabolic syndrome, n=111,505 for T2DM, and finally, n=114,491 for chronic inflammation.

Study participants provided informed written consent, and the study protocols were approved by the Institutional Review Boards of the MJ Health Management Institution and the National Health Research Institutes in Taiwan. Individual identification data were removed in the database, so that participants remained anonymous during the entire study

process [16]. To avoid research inaccuracies caused by the quality of the data, the MJ Health Research Foundation previously conducted a standardized data cleaning [17].

Main exposure variables

Body weight to the nearest 0.1 kg and height to the nearest mm were measured using an automatic anthropometer (Nakamura KN-5000A, Tokyo, Japan). Body mass index (BMI) was calculated as weight in kg divided by squared height in m. Since BMI is not a measure of body composition, we additionally included body fat percentage (BF%) assessed upright by foot-to-foot bioelectrical impedance analysis (TANITA® TBF models, Tokyo, Japan).

The time spent in leisure-time PA has been assessed by the MJ PA Questionnaire [13,18], which was included in the MJ health screening procedures since 1997. Participants were asked to report the intensity, frequency, and duration of PA during the last 4 weeks, with several examples of activity types given for four intensity categories: light (e.g. slow walking), moderate (e.g. brisk walking), medium-vigorous (e.g. jogging), or high-vigorous (e.g. running). A metabolic equivalent of task (MET; 3.5 ml/kg/min) value of 2.5 was assigned for light, 4.5 for moderate, 6.5 for medium-vigorous, and 8.5 for high-vigorous PA intensity. To calculate the total volume of PA (MET-h/week), the MET value for the reported intensity was multiplied by its frequency and duration. This questionnaire has shown good reliability and excellent convergent validity predicting cause-specific mortality and cancer incidence [18].

Change in BMI, BF% and PA as continuous variables was calculated as the difference between the first and second examinations, and divided by number of years between them because the interval between examinations varied among participants in this cohort. Participants were categorized into thirds of the annual changes in BMI and BF% variables for the analysis involving each CVD risk factor; the lowest and highest thirds represent weight or

fat ‘loss’ and ‘gain’, respectively, and the middle third a ‘stable’ condition. Participants with an annual PA change of 0 MET-h/week were categorized into the ‘no change’ group, whereas those with negative and positive values were categorized into the ‘decreasing’ and ‘increasing’ PA groups, respectively.

Ascertainment of CVD risk factors

Hypertension was identified from the medical history or as systolic/diastolic blood pressure ≥140/≥90 mm Hg. Hypercholesterolemia was also identified from the medical history or as serum total cholesterol ≥240 mg/dL. Atherogenic dyslipidemia was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria as triglycerides ≥150 mg/dL and HDL-C <40 mg/dL in men and <50 mg/dL in women [19]. Participants were also classified as having metabolic syndrome if they met ≥3 of the following criteria [19]: i) Asian-criteria: waist circumference ≥90 cm in men and ≥80 cm in women, ii) systolic/diastolic blood pressure ≥130/≥85 mmHg, or on medication, iii) triglycerides ≥150 mg/dL, iv) HDL-C <40 mg/dL in men or <50 mg/dL in women and v) fasting glucose ≥100 mg/dL or on medication. A systemic inflammatory status in the current study was defined as having C-reactive protein (CRP) ≥3 mg/L or white blood cells ≥12.1x10^3/μL [20]; the white blood cells cut-point was selected because it corresponds to the same percentile as the standardized CRP cut-point in the cohort (i.e. 99.5th). Follow-up time was computed as the difference between the date of the second examination and the date of the examination where each CVD risk factor or inflammation was developed for the first time or the last examination through the end of 2016.

Covariates

Participants reported their age, sex, educational attainment, and marital status. Information on smoking and alcohol consumption was based on standard questions. An optimal meal pattern was defined as an affirmative answer to the following question: “Do you eat on time and in regular amounts?” [13].

Statistical analysis

Baseline characteristics of the total sample according to changes in BMI (loss, stable, gain) and PA (decreasing, no change, increasing) were summarized as mean and standard deviation for continuous variables, and as percentage for categorical variables. Also we calculated the age- and sex-adjusted Pearson correlations between changes in BMI, BF% and PA.

To model the individual dose-response relationship between changes in BMI, BF% and PA and the subsequent development of CVD risk factors and inflammation, we used restricted cubic spline Cox regressions with knots at the 10th, 50th, and 90th percentile, and the lowest levels in these variables as the reference category. These continuous variables were previously truncated at the <1st and >99th percentile to minimize the influence of outliers. Also Cox regressions were used to estimate hazard ratios (HRs) and their 95% confidence interval (CI) for subsequent CVD risk factor and inflammation incidence according to changes in BMI, BF% and PA. We built two Cox models for these analyses. Model 1 was adjusted for age (years), sex (men, women), year of baseline examination (1997-2013), educational attainment (middle school or below, high school, junior school, college or above), marital status (married, single), BMI at baseline (<18.50, 18.50-22.99, 23.00-24.99, 25.00-26.99,≥27.00 kg/m^2), PA at baseline (0, 0.01-3.74, 3.75-7.49, 7.50-15.00, >15.00 MET-h/week), combined patterns of changes in smoking and alcohol drinking (never to never, never to current, past to past, past to current, current to past, current to current, never/past/current to missing indicator), meal patterns (optimal to suboptimal, optimal to

optimal, suboptimal to optimal, suboptimal to suboptimal, optimal/suboptimal to missing indicator), and baseline value or values of each CVD risk factor or inflammation (continuous variables). Model 2 was adjusted as model 1 plus changes in PA for BMI changes analyses or changes in BMI for PA changes analyses.

We finally examined the combined association of changes in BMI and PA with the development of CVD risk factors and inflammation by creating 9 exposure categories; the potentially healthier condition was the reference category (i.e. weight loss and increasing PA). In addition, and for public purposes, we also examined individual and combined associations of changes in BMI (remained non-obese, became non-obese, became obese, remained obese; obesity ≥25.00 kg/m^2) and PA (remained inactive, became inactive, became active, remained active; active ≥7.50 MET-h/week) status [9,21] with the development of CVD risk factors and inflammation, after adjustment for covariates, including number of years between baseline and second examinations.

The proportional hazards assumption was checked by assessing the log–log survival plots. Statistical significance was set at 2-sided $P< 0.05$. Analyses were performed with STATA v.14.

Results

At baseline, study participants had a mean±SD age of 37.8±11.5 years, 49% were women, 65% reported junior school or university studies, 66% were married, and mostly were never smokers (74%), never drinkers (83%) and with an optimal meal pattern (62%).

Table 1 shows the baseline characteristics of study participants according to changes in BMI and PA. On average, the interval between the first and second examinations was 1.9±1.6 years with an annual change in BMI, BF% and PA of 0.1±0.8 kg/m^2, 0.2±2.2 %, and 0.5±7.4 MET-h/week, respectively. Changes in PA showed only weak age- and sex-adjusted correlations with changes in BMI (r=-0.04, *P*<0.001) and BF% (r=-0.05, *P*<0.001). As expected, changes in BMI and changes in BF% were strongly correlated (r=0.64, *P*<0.001).

During an average follow-up of 5.7±4.1 years after the second examination, 10840 individuals (11.1%) developed hypertension, 10888 (11.0%) hypercholesterolemia, 6078 (6.5%) atherogenic dyslipidemia, 13223 (14.2%) metabolic syndrome, 4816 (4.3%) T2DM, and 2027 (1.8%) inflammation. The corresponding incidence rates were 19.5, 19.7, 11.4, 25.4, 7.3, and 3.0 per 1,000 person-years.

Restrictive cubic spline models (Figure 1) showed a clear positive non-linear dose-response association between changes in BMI and subsequent incidence of all CVD risk factors (all *P* for non-linear trend <0.001). Similar results were found for change in BF% (Supplementary Figure 1). Changes in PA showed significant non-linear dose-response associations (Figure 2) with subsequent incidence of hypertension, atherogenic dyslipidemia, and metabolic syndrome (all *P* for non-linear trend <0.05). The association between changes in PA and incident T2DM was not non-linear (*P* for non-linear trend =0.13) but linear (*P* for linear trend=0.019).

Weight gain was associated with a subsequent higher risk of all CVD risk factors, with HR (95%CI) ranging from 1.11 (1.00-1.23) for inflammation to 1.74 (1.67-1.82) for

metabolic syndrome, compared with participants who lost weight (Table 2). A stable weight was also associated with a higher risk of all CVD risk factors except with inflammation; HR (95%CI) ranging from 1.07 (1.00-1.15) for atherogenic dyslipidemia to 1.25 (1.16-1.34) for T2DM. Compared to decreasing PA, an increase in PA was associated with a subsequent lower risk of hypertension, atherogenic dyslipidemia, metabolic syndrome and T2DM, with HR (95% CI) ranging from 0.87 (0.81-0.94) for T2DM to 0.94 (0.89-0.99) for hypertension. Also, no change in PA was linked to lower risk of T2DM (Table 2). Results were similar in analyses using changes in BF% as the exposure (Supplementary Table 1).

Results for the combined association between changes in BMI and PA with subsequent incidence of CVD risk factors showed that participants who gained weight and decreased PA levels had the highest risk compared with those who lost weight and increased PA (Figure 3). Increasing or maintaining PA levels reduced the increased subsequent risk of some CVD risk factors among participants who maintained a stable weight or gained weight (Figure 4 and Supplementary Figure 2). Among participants who lost weight, decreased PA was not associated with an increased risk of most CVD risk factors (Figure 3).

Individual analyses by changes in BMI categories at the first and second examinations showed higher incidence of CVD risk factors among participants who became or remained obese compared with those who remained non-obese (Supplementary Table 2). Among these participants with an increased risk, those who remained active or became active notably reduced the incidence of some CVD risk factors (Supplementary Table 3).

Discussion

In this large prospective cohort of Asian men and women, weight loss was consistently associated with a lower incidence of major CVD risk factors. Also, after accounting for many confounders, including changes in other lifestyle behaviors and simultaneous changes in body weight, maintaining or increasing PA was associated with less frequent development of some major CVD risk factors, such as hypertension, atherogenic dyslipidemia, metabolic syndrome and T2DM. Of note was that the cardioprotective effects of PA were observed mostly in people who maintained or gained weight. Since many people who start to exercise, with weight loss as the primary goal, get disappointed when they fail to lose weight and, then, quit, our findings send an important message to these people to keep exercising or being physically active, because they suggest that PA contributes to CVD primordial prevention even if weight loss is not achieved.

Data on the health risks of obesity has been conflicting, for example, with literature on the existence or not of a metabolically healthy obesity [22-24]. Our study confirms that obesity and its changes over time are tightly related to the development of CVD risk factors. In fact, for a given baseline weight status, and compared to weight loss, weight maintenance was associated with a higher risk of development of CVD risk factors. Hence, weight loss is clearly an important goal for primordial prevention in apparently healthy populations [4,5,7]. However, at population level, the obesity epidemic continues to increase in many countries or at best has leveled-off [25,26]. In addition, most clinical trials indicate that significant weight loss can be achieved in many people but it is maintained only in a few of them [27,28]. In this scenario, lifestyle modification, either improving diet or PA, is crucial for preventing CVD risk factors [23,24].

In a prior work with data from almost 200,000 individuals in this same cohort [13], we found that PA was associated with lower incidence of hypertension, atherogenic dyslipidemia,

metabolic syndrome and T2DM, regardless of BMI. In addition, our results showed that even lower volumes of PA than those currently recommended prevented CVD risk factors. Results of this current analysis extend knowledge in this field by showing that PA change reduces the incidence of CVD risk factors, independently of baseline and simultaneous changes in BMI or BF%. Lee et al. [29] examined the association of changes in PA and incidence of hypertension and T2DM in 113,087 individuals in the South Korea Kangbuk Samsung Hospital cohort; compared to decreasing PA, increasing PA was negatively associated with both outcomes (HR, 0.93, 95%CI: 0.87-0.99 for hypertension and 0.83, 95%CI: 0.74-0.92 for T2DM), and no change in PA with lower risk of T2DM (HR, 0.89, 95%CI:0.81-0.97). However, simultaneous changes in body fat variables were not taken into account and part of the effect of PA on hypertension and T2DM could be mediated by its direct role on weight change. In small exercise-based clinical trials among patients unable to lose weight, increased PA led to some improvement in abdominal fat, cardiorespiratory fitness, insulin sensitivity, vascular compliance, endothelial function, and lipoprotein particle size [12].

The modulatory effects of PA on cardiovascular health are complex and not completely elucidated. PA is associated with improvements in CVD risk factors, but these benefits may result from improvements in cardiorespiratory fitness through increased PA, which is a stronger predictor of CVD outcomes than PA alone [30,31]. In addition, although there are cardiorespiratory fitness variations by sex, age and genetic background, high levels of fitness are associated with lower risk of CVD risk factors such as obesity, hypertension, metabolic syndrome and T2DM [32].

The major strength of our study was the inclusion of a large number of participants with a wide age range, a long follow-up period, objective measurements of major CVD risk factors and inflammation markers, and repeated assessments of exposure and outcome variables. The current study also has several limitations. PA was self-reported, which

regularly overestimates PA levels and underestimates the true effect of the associations; thus further evidence with objective measures of PA should be obtained in future research. Also, PA was limited to the leisure-time domain, so the dose-response association of changes in PA in other domains (i.e., occupational, household and transportation) with incidence of CVD risk factors regardless of body weight changes should still be investigated. Lack of data on other potentially important variables (e.g. family history of CVD, food intake, over-the-counter medications) is also a limitation in the present work. In addition, study participants may not be representative of the general population of Taiwan, because they had slightly higher socioeconomic status; however, the prevalence of CVD risk factors and other characteristics in this cohort were similar to that in the Taiwanese population [14]. Thus, our analyses should be replicated in other Asian and non-Asian cohorts. Finally, as in any observational study, some residual confounding cannot be ruled out despite adjustment for many variables, including simultaneous changes in lifestyle behaviors.

In conclusion, although weight loss is crucial for the prevention of CVD risk factors, increasing or maintaining PA is also important to prevent them among adults who gain or maintain their weight. Pragmatically, primordial CVD prevention should be based on promoting healthy lifestyle behaviors such as a PA, because it influences not only both weight status but also cardiorespiratory fitness and other CVD health outcomes.

Financial support

This work was supported by Grant 02/2014 from the *Plan Nacional sobre Drogas* (Ministry of Health of Spain), FIS grants 12/1166 and 16/609 (State Secretary of R+D+I and FEDER/FSE), and MINECO R+D+I grant (DEP2013-47786-R). DM-G is supported by a 'Ramon y Cajal' contract (RYC-2016-20546). The MJ cohort was supported by the MJ Health Management Institution. All data used in this research were authorized by, and received from MJ Health Research Foundation by MJ Health Research Center (Authorization Codes: MJHRF2017006A and MJHRF2017007A). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We thank MJ Health Research Foundation for making their large dataset available to us.

Author contributions

DMG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: DMG, FBO, MH, and CJL. Analysis and interpretation of data: all authors. Drafting of the manuscript: DMG, FBO, MH, CJL, and FRA. Critical revision of the manuscript for important intellectual content: FBO, MH, VCS, ES, EGS, HPG, KPS, and CJL. Statistical analysis: DMG, FBO, and MH. Administrative, technical, or material support: EGS, ES, VCS, HPG and KPS. Study supervision: CJL and FRA. All authors have read and approved the final manuscript.

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Figure legends

Figure 1. Incidence of cardiovascular disease risk factors according to changes in body mass index, based on restricted cubic splines with knots at the 10th, 50th, and 90th percentile of the body mass index distribution. Solid lines indicate hazard ratios and dashed lines indicate 95% confidence intervals. Analyses were adjusted for age, sex, year of baseline examination, educational attainment, marital status, body mass index at baseline, physical activity at baseline, changes in smoking, alcohol drinking, meal patterns and physical activity, and baseline value or values of each cardiovascular disease risk factor or inflammation markers.

Figure 2. Incidence of cardiovascular disease risk factors according to changes in physical activity, based on restricted cubic splines with knots at the 10th, 50th, and 90th percentile of the physical activity distribution. Solid lines indicate hazard ratios and dashed lines indicate 95% confidence intervals. Analyses were adjusted for age, sex, year of baseline examination, educational attainment, marital status, body mass index at baseline, physical activity at baseline, changes in smoking, alcohol drinking, meal patterns and body mass index, and baseline value or values of each cardiovascular disease risk factor or inflammation markers.

Figure 3. Combined association of changes in body mass index and physical activity with the subsequent incidence of cardiovascular disease risk factors. Analyses were adjusted for age, sex, year of baseline examination, number of years between baseline and second examinations, educational attainment, marital status, body mass index at baseline, physical activity at baseline, changes in smoking, alcohol drinking, meal patterns, and baseline value or values of each cardiovascular disease risk factor or inflammation markers.

Figure 4. Association of changes in physical activity with the subsequent incidence of cardiovascular disease risk factors among individuals without weight loss. Analyses were adjusted for age, sex, year of baseline examination, educational attainment, marital status, body mass index at baseline, physical

activity at baseline, changes in smoking, alcohol drinking, meal patterns, and baseline value or values of each cardiovascular disease risk factor or inflammation markers. Individuals who maintained a stable weight or gained weight were included.

Table 1. Baseline characteristics of study participants according to changes in body mass index and physical activity during follow-up.

	Change in body mass index				Change in physical activity			
	Loss	Stable	Gain	*P*	Decreasing	No change	Increasing	*P*
N	38713	38713	38708		37256	32654	46224	
Women	49.9	49.9	47.0	<0.001	45.2	52.6	49.3	<0.001
Age, y	39.5±12.2	37.7±11.2	36.4±10.8	<0.001	37.6±11.7	37.4±10.9	38.5±11.6	<0.001
Educational attainment, %				<0.001				
Middle school or below	16.9	13.6	11.8		13.1	13.8	15.1	
High school	20.2	20.5	19.9		18.7	22.0	20.1	
Junior school	23.1	25.0	25.5		23.4	26.3	24.3	
College or above	39.8	40.9	42.8	<0.001	44.8	37.9	40.5	<0.001
Married, %	68.8	67.6	62.2	<0.001	62.6	68.2	67.6	<0.001
Smoking status, %								
Never	74.3	74.7	72.5		73.1	74.3	74.2	
Former	6.5	5.6	6.0		6.3	5.5	6.1	
Current	19.2	19.7	21.5	<0.001	20.6	20.2	19.7	0.015
Alcohol drinking, %								
Never	82.7	83.2	82.9		82.2	84.0	82.8	
Former	2.1	2.0	2.3		2.2	2.0	2.2	
Current	15.2	14.8	14.8	0.518	15.6	14.0	15.0	0.223
Optimal meal patterns, %	63.2	62.3	59.0	<0.001	62.9	59.0	62.0	0.109
Body mass index, kg/m^2	23.4±3.5	22.2±3.2	22.6±3.5	<0.001	22.8±3.4	22.5±3.5	22.8±3.4	0.257
Body fat*, %	26.6±6.7	24.6±6.2	25.0±6.6	<.001	25.1±6.5	25.4±6.6	25.6±6.6	<0.001
Physical activity, MET-h/week	6.2±9.2	5.8±8.9	5.7±8.9	<0.001	10.8±11.6	3.3±6.6	3.7±6.2	<0.001
Hypertension, %	15.9	11.4	11.0	<0.001	12.7	11.7	13.6	<0.001
Hypercholesterolemia, %	12.0	9.3	8.6	<0.001	9.7	9.6	10.5	<0.001
Waist circumference, cm	77.9±10.3	75.1±9.9	75.8±10.0	<0.001	76.5±10.0	75.7±10.3	76.5±10.2	0.747
HDL-cholesterol, mg/dL	52.3±14.9	53.6±15.1	53.4±15.0	<0.001	53.3±14.9	52.8±14.9	53.0±15.1	0.036
Triglycerides, mg/dL	122.4±101.1	108.0±82.0	103.6±75.8	<0.001	109.7±84.7	110.7±86.8	113.1±89.7	<0.001
Type 2 diabetes, %	4.3	2.2	1.9	<0.001	2.7	2.7	3.0	0.033
C-reactive protein, mg/dL	0.2±0.4	0.2±0.4	0.2±0.5	0.126	0.2±0.4	0.2±0.4	0.2±0.5	<0.001
White blood cells, $x10^3/\mu L$	6.3±1.6	6.1±1.5	6.2±1.6	0.103	6.1±1.5	6.2±1.6	6.2±1.6	<0.001

Values are mean±SD or %. *n=115,

Table 2. Association of changes in body mass index and physical activity with the subsequent incidence of cardiovascular disease risk factors

	Body mass index change			Physical activity change		
	Loss	Stable	Gain	Decreasing	No change	Increasing
Incident hypertension						
N/cases	32481/3532	32463/3459	32472/3849	31283/3424	27834/3138	38299/4278
Model 1 HR (95%CI)	1 (Reference)	**1.25 (1.19-1.31)**	**1.39 (1.33-1.46)**	1 (Reference)	0.97 (0.92-1.02)	**0.93 (0.89-0.98)**
Model 2 HR (95%CI)	1 (Reference)	**1.25 (1.19-1.31)**	**1.40 (1.33-1.46)**	1 (Reference)	0.97 (0.92-1.03)	**0.94 (0.89-0.99)**
Incident hypercholesterolemia						
N/cases	32947/3665	32945/3514	32945/3709	31713/3404	28040/3190	39084/4294
Model 1 HR (95%CI)	1 (Reference)	**1.12 (1.07-1.17)**	**1.21 (1.16-1.27)**	1 (Reference)	0.98 (0.93-1.04)	0.97 (0.92-1.02)
Model 2 HR (95%CI)	1 (Reference)	**1.12 (1.07-1.17)**	**1.21 (1.15-1.27)**	1 (Reference)	0.98 (0.93-1.04)	0.97 (0.93-1.03)
Incident atherogenic dyslipidemia						
N/cases	31273/1966	31236/1747	31234/2365	30264/1888	26224/1822	37219/2368
Model 1 HR (95%CI)	1 (Reference)	**1.08 (1.01-1.15)**	**1.45 (1.36-1.53)**	1 (Reference)	0.97 (0.90-1.05)	**0.90 (0.84-0.97)**
Model 2 HR (95%CI)	1 (Reference)	**1.07 (1.00-1.15)**	**1.44 (1.35-1.53)**	1 (Reference)	0.97 (0.90-1.04)	**0.91 (0.85-0.98)**
Incident metabolic syndrome						
N/cases	31022/4048	31034/3873	31010/5302	30025/4203	26429/3908	36612/5112
Model 1 HR (95%CI)	1 (Reference)	**1.30 (1.24-1.35)**	**1.75 (1.68-1.82)**	1 (Reference)	0.99 (0.94-1.04)	**0.90 (0.86-0.94)**
Model 2 HR (95%CI)	1 (Reference)	**1.29 (1.24-1.35)**	**1.74 (1.67-1.82)**	1 (Reference)	1.00 (0.95-1.05)	**0.91 (0.87-0.96)**
Incident type 2 diabetes						
N/cases	37172/1627	37168/1440	37165/1749	35788/1495	31432/1400	44285/1921
Model 1 HR (95%CI)	1 (Reference)	**1.25 (1.16-1.34)**	**1.48 (1.38-1.58)**	1 (Reference)	**0.89 (0.82-0.97)**	**0.86 (0.80-0.93)**
Model 2 HR (95%CI)	1 (Reference)	**1.25 (1.16-1.34)**	**1.47 (1.37-1.58)**	1 (Reference)	**0.89 (0.82-0.96)**	**0.87 (0.81-0.94)**
Incident inflammation						
N/cases	38164/703	38164/589	38163/735	36095/635	32169/592	44792/800
Model 1 HR (95%CI)	1 (Reference)	0.95 (0.85-1.06)	**1.10 (1.00-1.22)**	1 (Reference)	1.02 (0.89-1.16)	1.00 (0.89-1.13)
Model 2 HR (95%CI)	1 (Reference)	0.95 (0.85-1.06)	**1.11 (1.00-1.23)**	1 (Reference)	1.02 (0.90-1.16)	1.00 (0.89-1.14)

HR: Hazard ratio; CI: Confidence interval. Model 1 was adjusted for age, sex, year of baseline examination, educational attainment, marital status, body mass index at baseline, physical activity at baseline, changes in smoking, alcohol drinking, meal pattern, physical activity at baseline, and baseline value or values of each cardiovascular disease risk factor or inflammatory markers. Model 2 was adjusted as model 1 plus changes in physical activity for body mass index changes analyses or changes in body mass index for physical activity changes analyses.