Changes in physical activity and adiposity with mortality and incidence of cardiovascular disease: longitudinal findings from the UK Biobank

Supplemental Document

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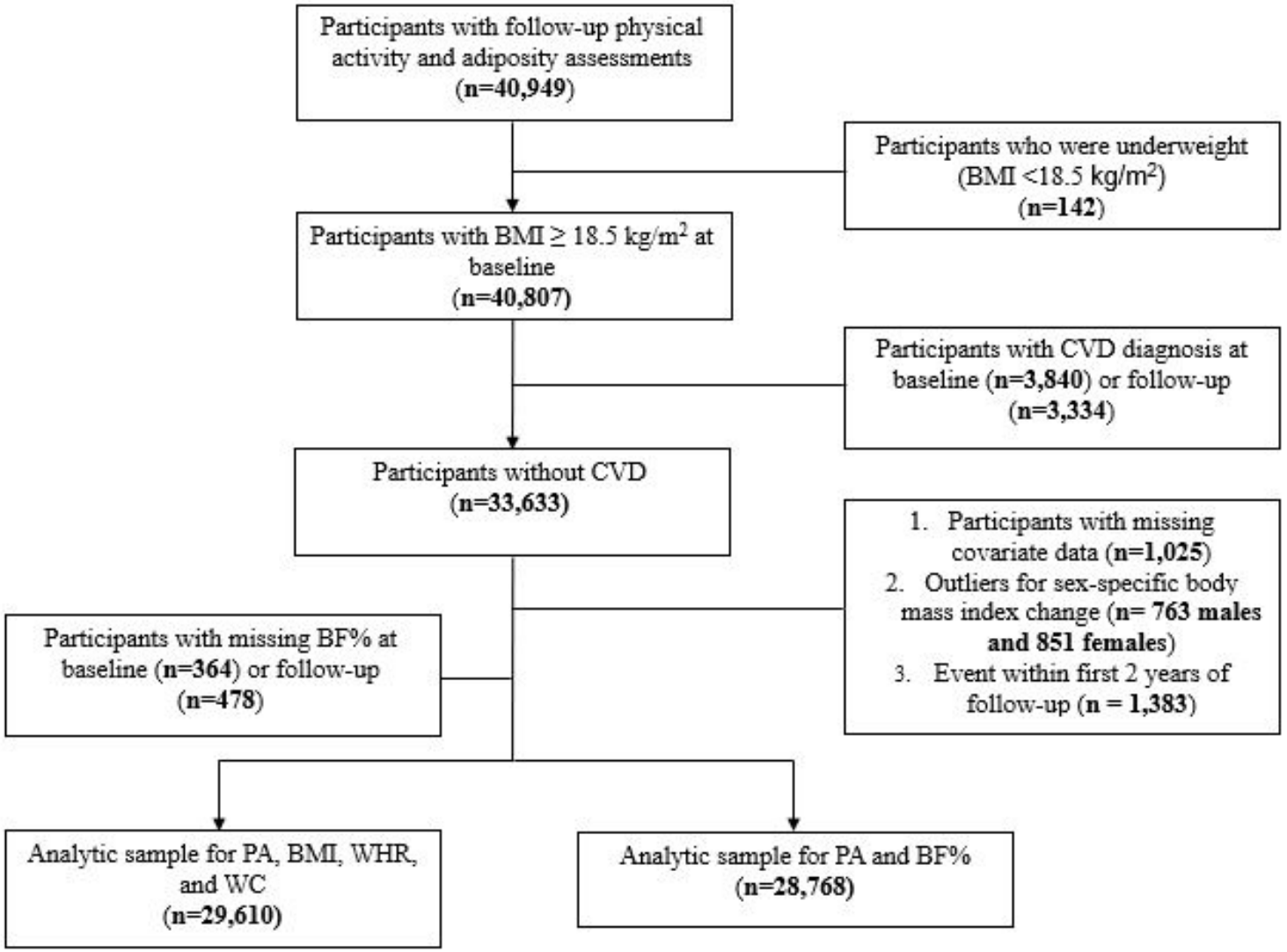
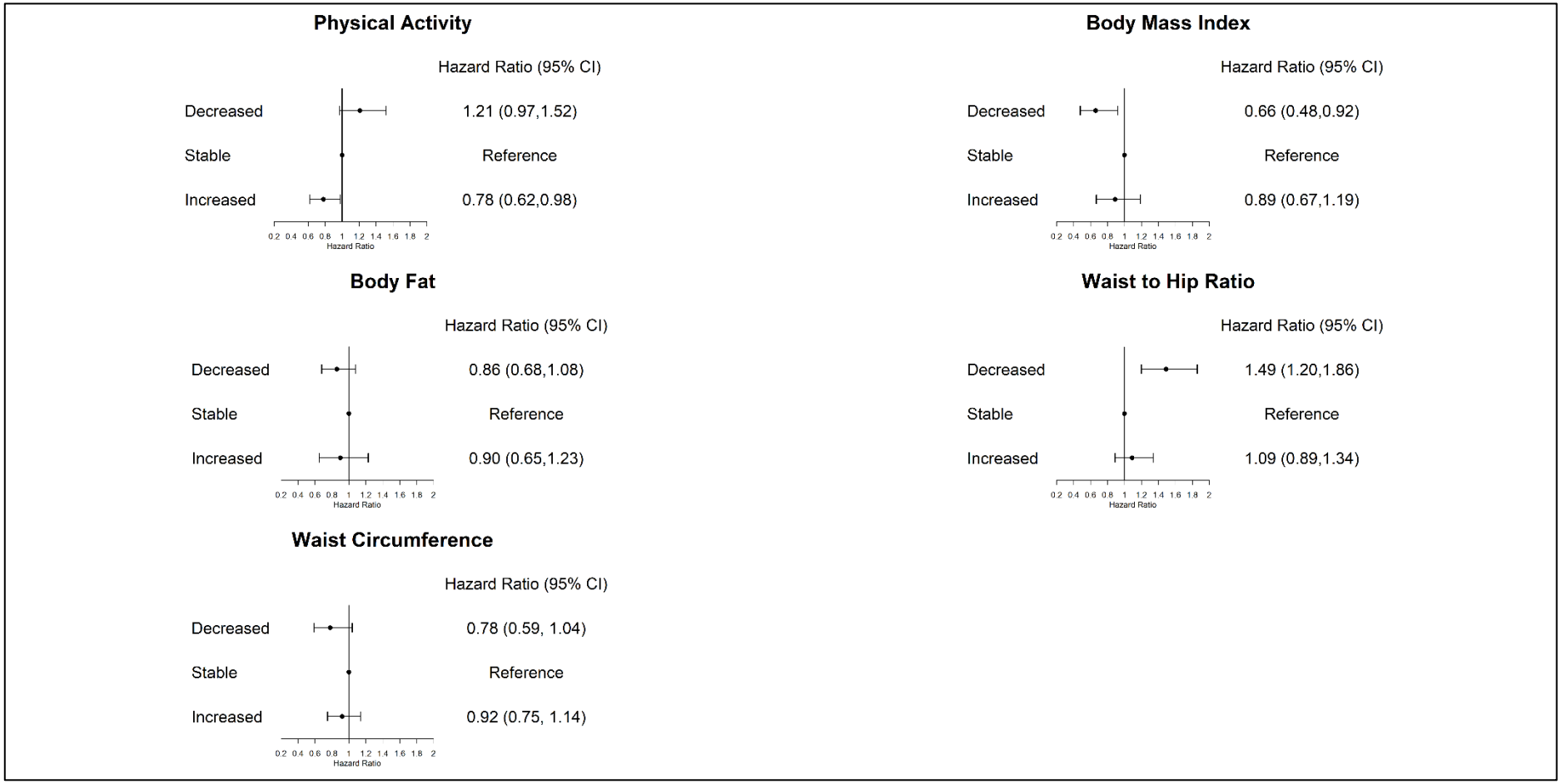
Supplemental Figure 1: Flow diagram of participants in the study

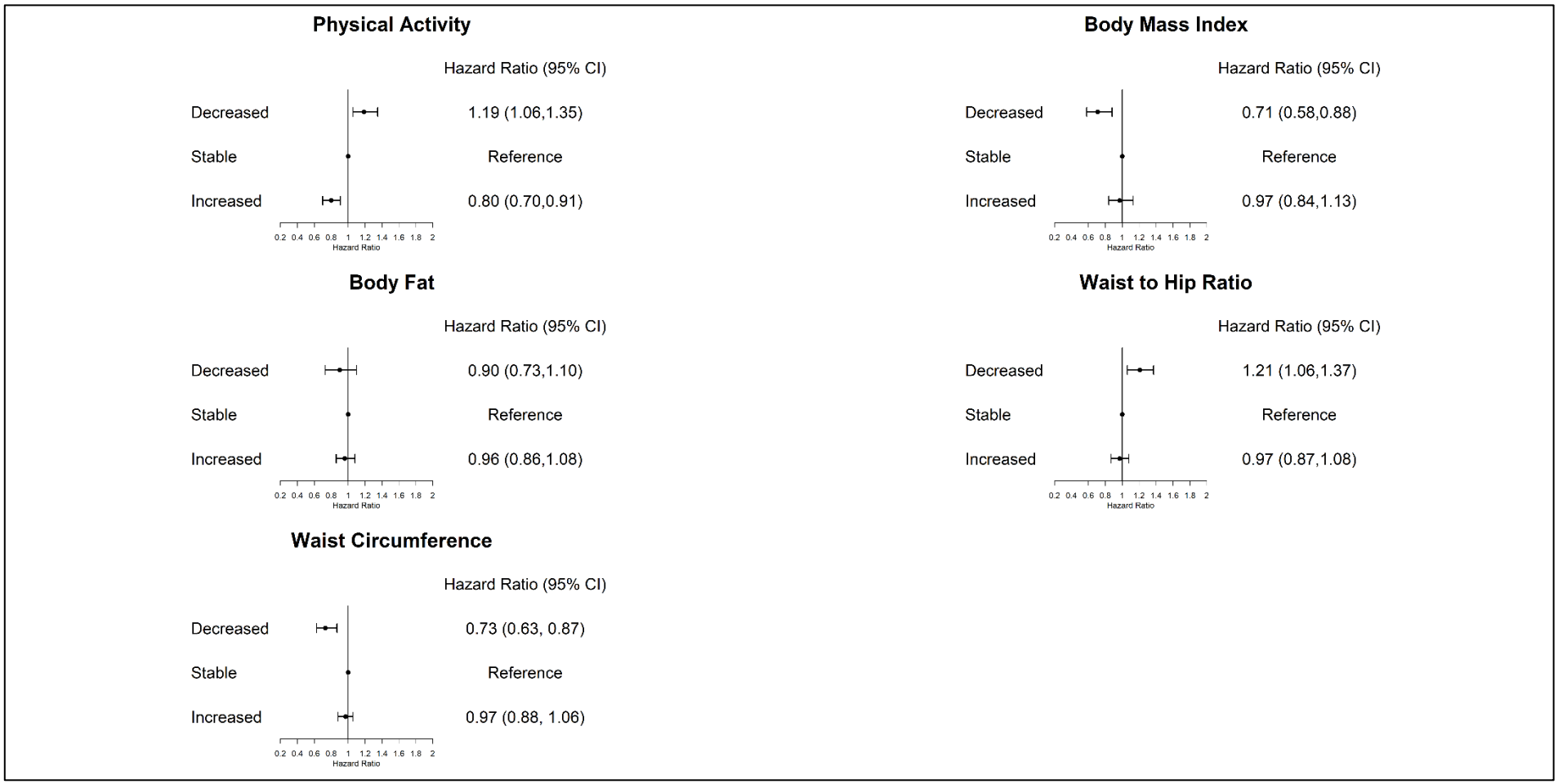


Supplemental Figure 2: Independent association of changes in physical activity and indicators of adiposity with all-cause mortality (physical activity, body mass index and waist to hip ratio [n=29,610]; body fat percentage [n=28,768]).



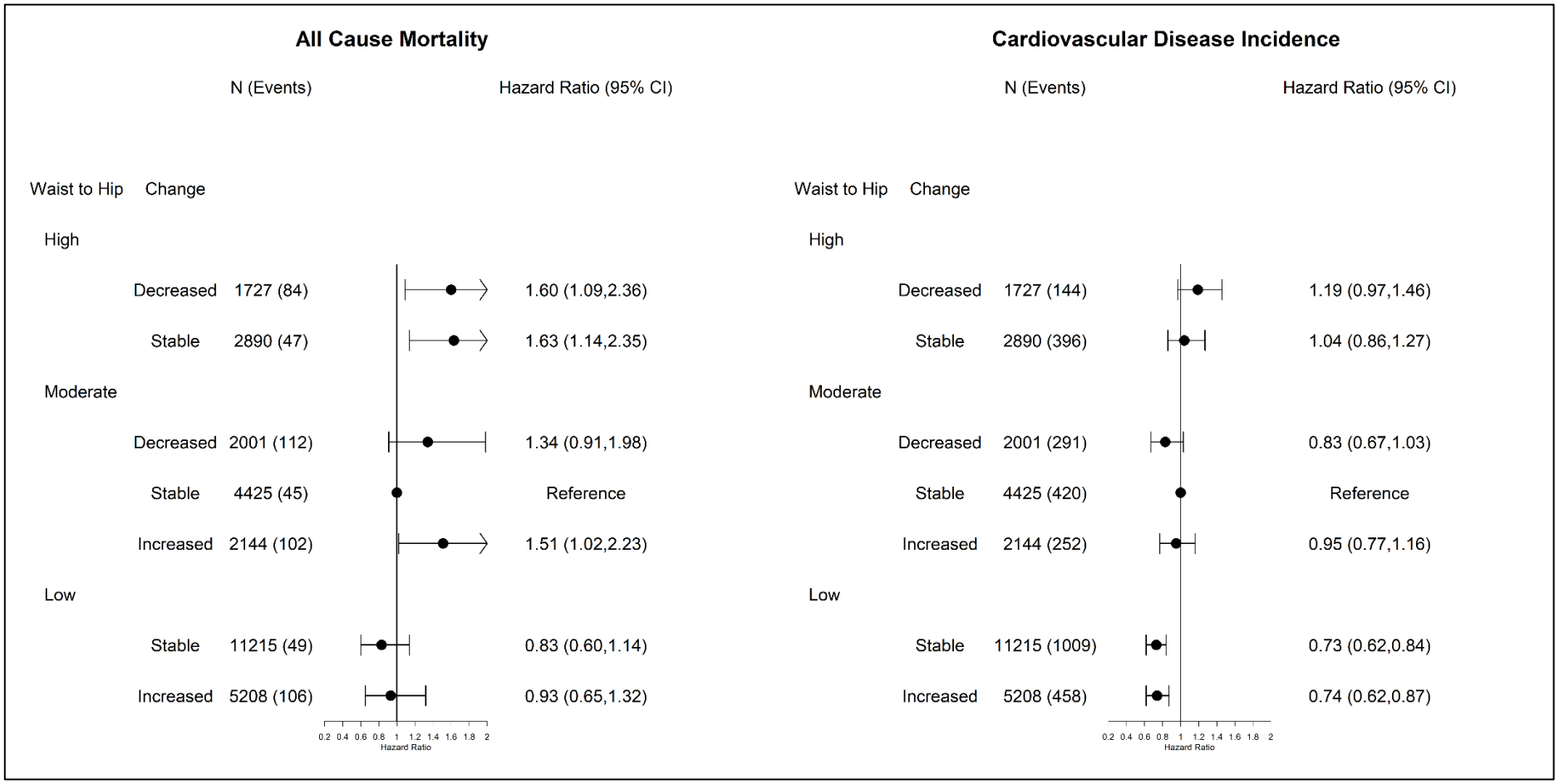
Adjusted for age, sex, physical activity baseline and change group (or body mass index baseline and change group for physical activity as an exposure); smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis

Supplemental Figure 3: Independent association of changes in physical activity and indicators of adiposity with cardiovascular disease (physical activity, body mass index and waist to hip ratio [n=29,610]; body fat percentage [n=28,768]).



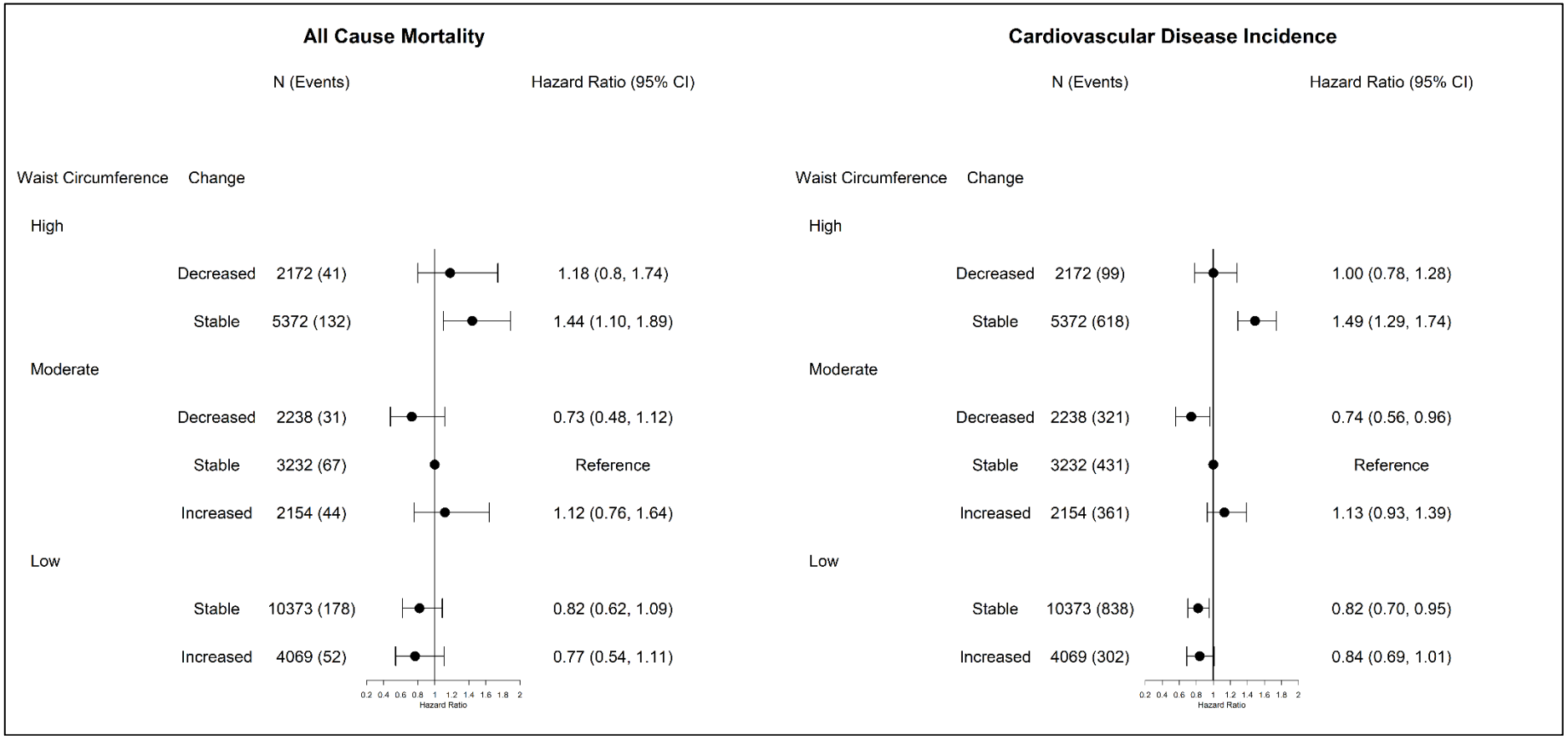
Adjusted for age, sex, physical activity baseline and change group (or body mass index baseline and change group for physical activity as an exposure); smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis

Supplemental Figure 4: Joint association of changes in baseline waist to hip ratio (n=29,610).



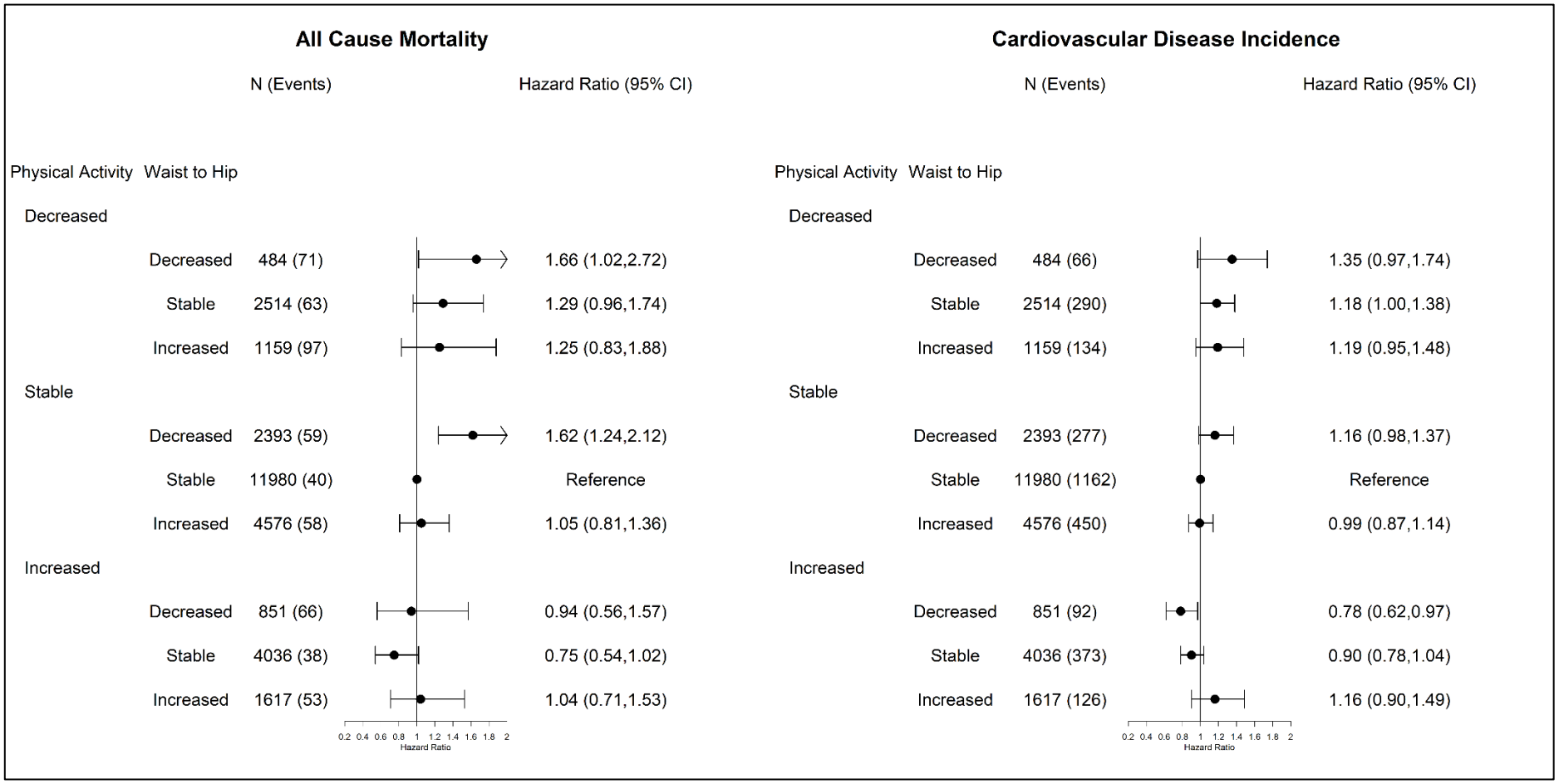
WHR (waist to hip ratio): High ≥ 1.0 for men and ≥ 0.86 for women; Moderate ≥ 0.96 for men and ≥ 0.81 for women; adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, physical activity baseline group, deprivation index, and cancer diagnosis

Supplemental Figure 5: Joint association of changes in baseline waist circumference (n=29,610).



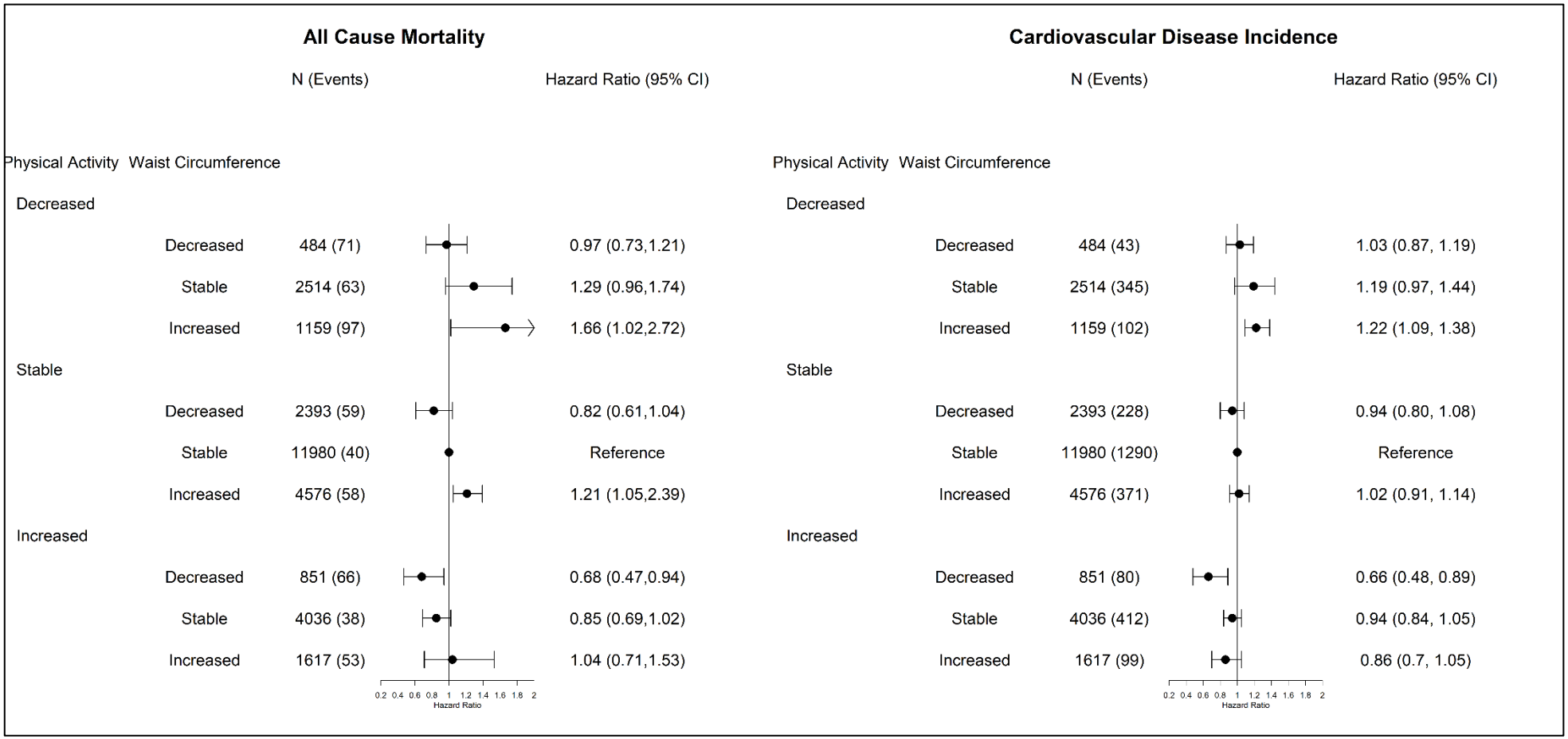
High: > 102cm for men and >88cm for women; Moderate: ≤102cm to > 94cm for men and ≤88cm to > 80cm for women; adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, physical activity baseline group, deprivation index, and cancer diagnosis

Supplemental Figure 6: Joint association of changes in physical activity and waist to hip ratio (n=29,610).



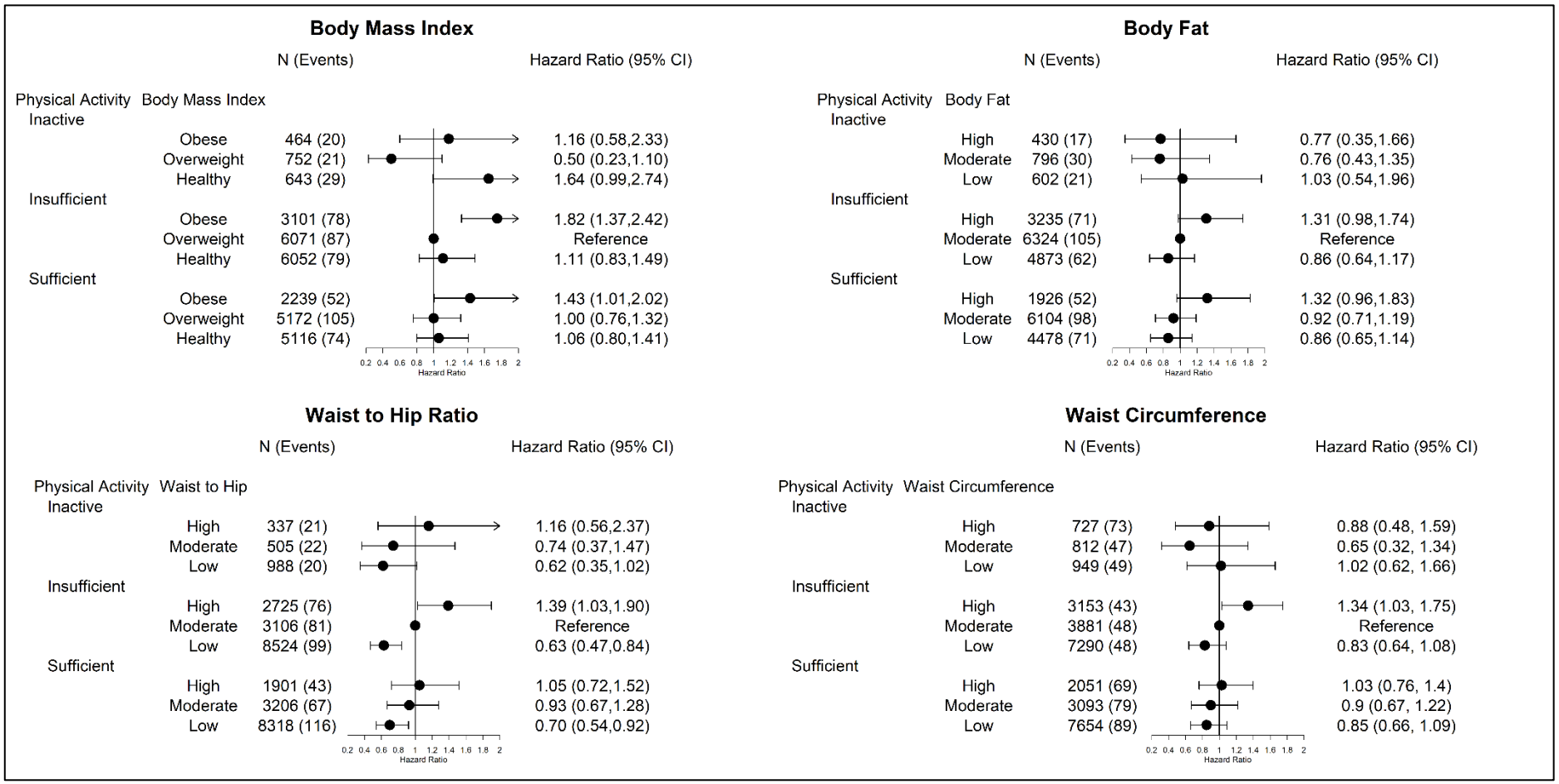
Adjusted for age, sex, baseline physical activity group, baseline waist to hip ratio group; smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis.

Supplemental Figure 7: Joint association of changes in physical activity and waist circumference (n=29,610).



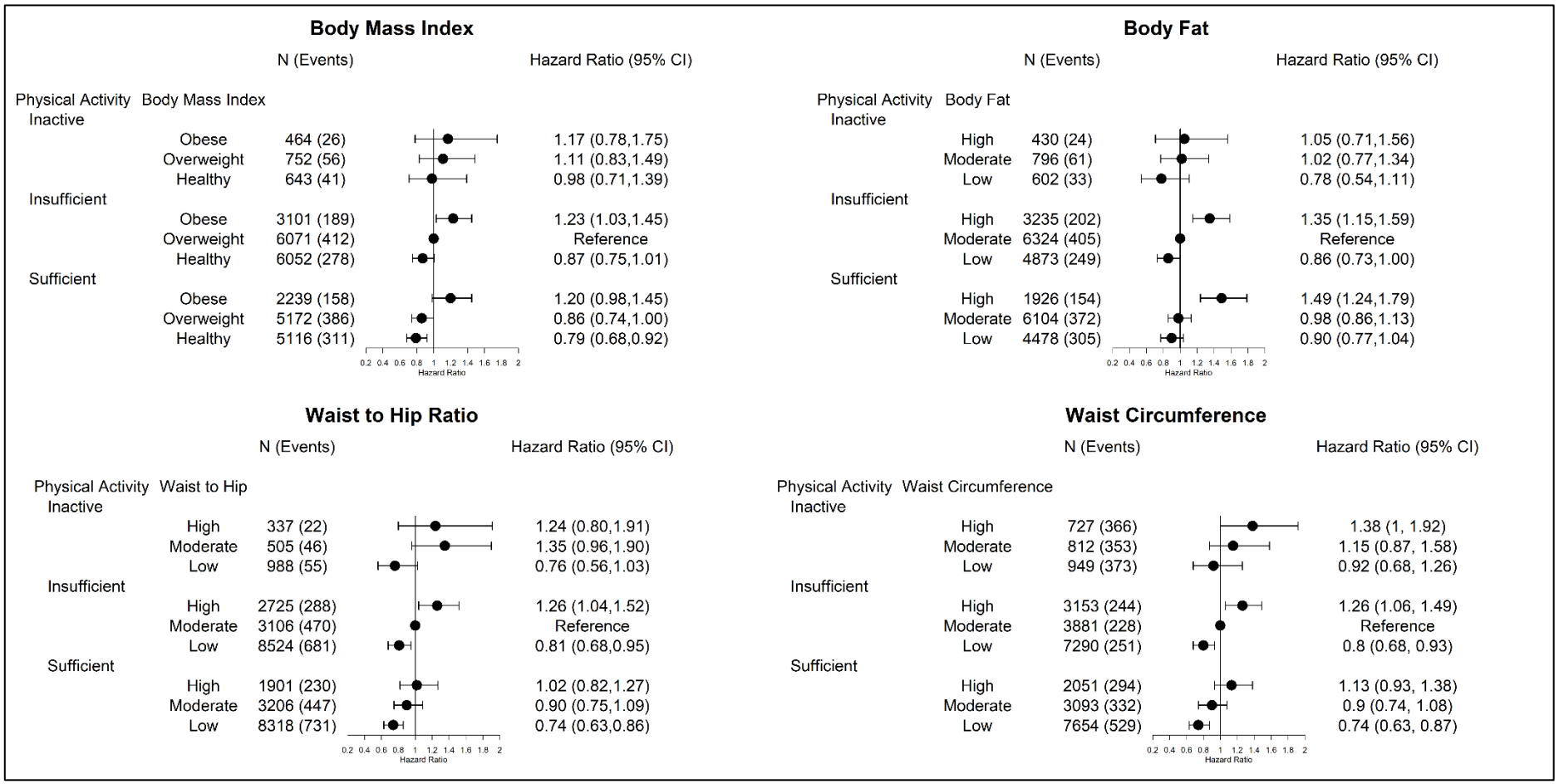
Adjusted for age, sex, baseline physical activity group, baseline waist circumference group; smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis.

Supplemental Figure 8: Joint association of baseline physical activity and indicators of adiposity with all-cause mortality (body mass index, waist circumference, and waist to hip ratio [n=29,610]; body fat percentage [n=28,768]).



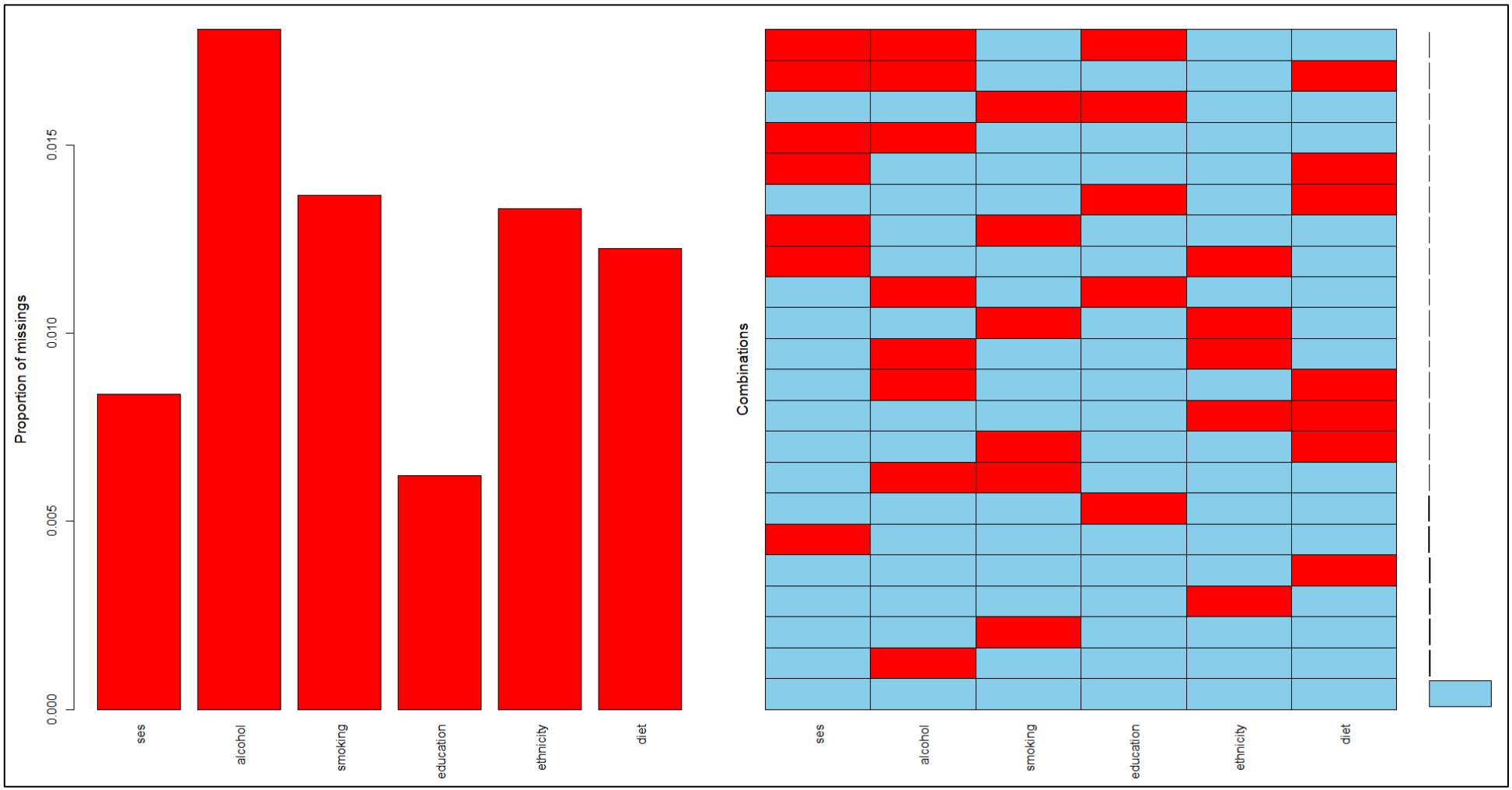
Physical activity: inactive (0 minutes of MVPA), Insufficient (>0 to < 150 minutes of MVPA), Sufficient (≥ 150 minutes of MVPA); Body mass index: obese (≥ 30 kg/m^2), overweight (<30 to ≥ 25 kg/m^2), or healthy weight (≥ 18.5 kg/m^2; %body fat:: high (≥29% for men and ≥42% for women), moderate(<29% to ≥22% for men and <42% to ≥35.2% for women), and low(<22% for men and <35.2% for women).; WHR (waist to hip ratio): High ≥ 1.0 for men and ≥ 0.86 for women; Moderate ≥ 0.96 for men and ≥ 0.81 for women; Adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis

Supplemental Figure 9: Joint association of baseline physical activity and indicators of adiposity with cardiovascular disease incidence (body mass index, waist circumference, and waist to hip ratio [n=29,610]; body fat percentage [n=28,768]).



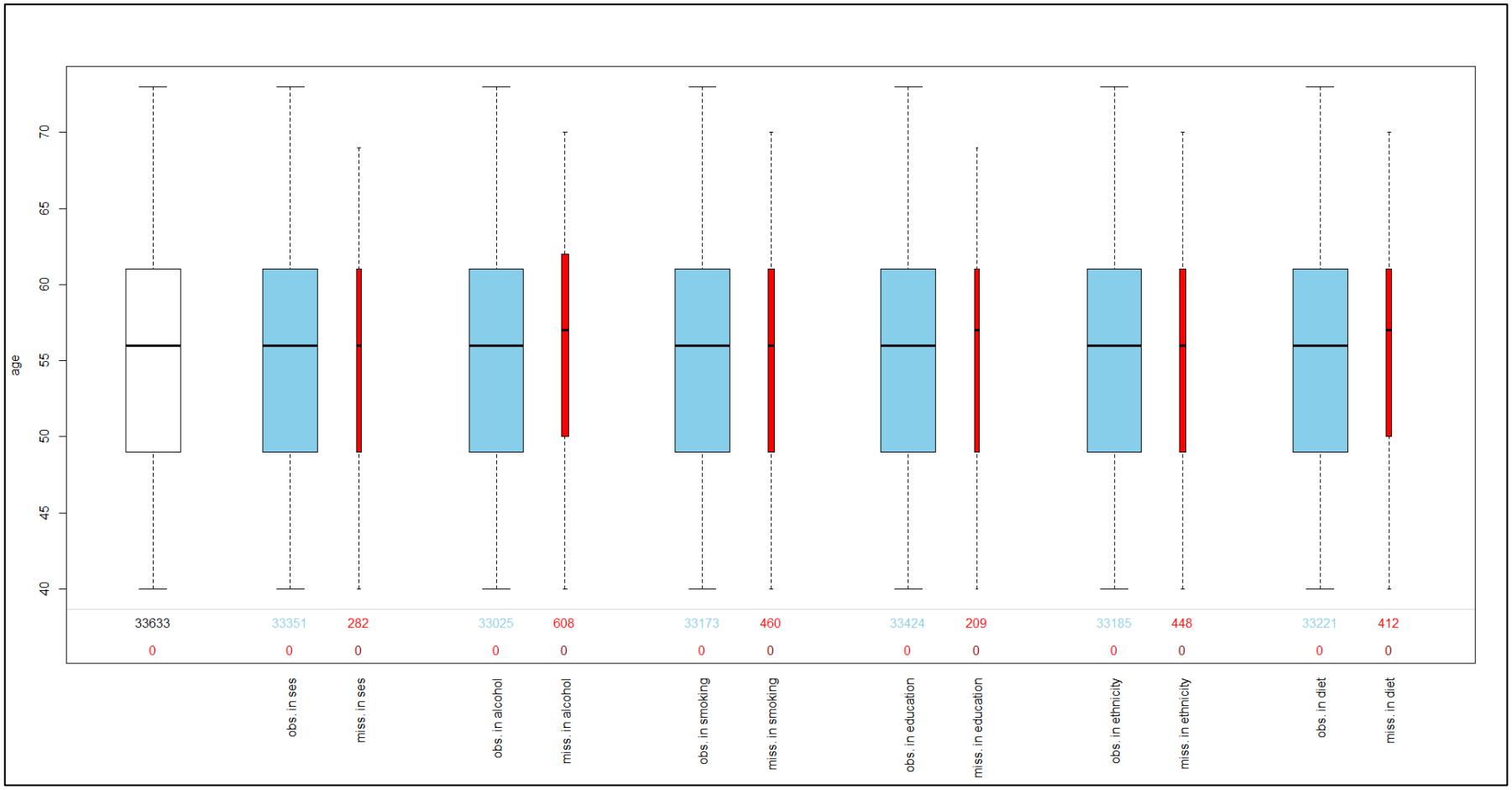
Physical activity: inactive (0 minutes of MVPA), Insufficient (>0 to < 150 minutes of MVPA), Sufficient (≥ 150 minutes of MVPA); Body mass index: obese (≥ 30 kg/m^2), overweight (<30 to ≥ 25 kg/m^2), or healthy weight (≥ 18.5 kg/m^2; %body fat:: high (≥29% for men and ≥42% for women), moderate(<29% to ≥22% for men and <42% to ≥35.2% for women), and low(<22% for men and <35.2% for women).; WHR (waist to hip ratio): High ≥ 1.0 for men and ≥ 0.86 for women; Moderate ≥ 0.96 for men and ≥ 0.81 for women; Adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis

Supplemental Figure 10: Distributions and combinations of unobserved lifestyle covariate data in the eligible sample of 33,633 participants.



Barplots (left side of figure) depict the proportion of covariates with missing data and the combination matrix (right side of figure) depicts the combinations of missing data across covariates; horizontal barplot next to the combination matrix depicts the proportion of data for a particular combination.

Supplemental Figure 11: Observed and unobserved lifestyle covariate data distributions relative to participant age in the eligible sample of 33,633 participants



Box plots depict the distribution of observed (blue) and unobserved (red) data for covariates across age distribution (white) in the eligible sample. The median and IQR of the unobserved (missing) data boxplots being within the IQR of observed data boxplots is an indication that the assumption of missing completely at random (MCAR) is met.

Supplemental Table 1: Participant follow-up characteristics categorized by physical activity and body mass index groups (n = 29,610)

Physical activity group	Increase			Stable			Decrease		
BMI group	Increase	Stable	Decrease	Increase	Stable	Decrease	Increase	Stable	Decrease
Education = college/university, N (%)	365 (57.5)	2736 (51.3)	235 (46.0)	1184 (57.7)	8178 (51.9)	569 (53.2)	342 (61.5)	1913 (56.1)	101 (57.1)
Smoking, N (%)									
never	358 (56.6)	3427 (64.4)	319 (62.7)	1284 (62.7)	10082 (64.1)	661 (61.9)	326 (58.7)	2116 (62.2)	112 (63.3)
previous	249 (39.3)	1712 (32.2)	164 (32.2)	679 (33.2)	5012 (31.9)	384 (36.0)	203 (36.6)	1119 (32.9)	56 (31.6)
current	26 (4.1)	184 (3.5)	26 (5.1)	84 (4.1)	628 (4.0)	22 (2.1)	26 (4.7)	167 (4.9)	9 (5.1)
Alcohol consumption, units/week[1]	4.12 (1.18)	4.12 (1.13)	4.16 (1.15)	4.12 (1.19)	4.13 (1.13)	4.16 (1.10)	4.01 (1.23)	4.08 (1.18)	4.04 (1.08)
Fruits and vegetables, servings per day	5.14 (7.69)	5.85 (7.21)	5.86 (6.14)	5.96 (7.99)	6.27 (7.63)	6.87 (7.43)	5.99 (7.05)	5.79 (7.49)	5.75 (7.10)
Sleep pattern, N (%)[2]									
Poor	13 (3.9)	37 (1.4)	3 (1.3)	26 (1.9)	109 (1.2)	3 (0.5)	5 (1.5)	17 (1.0)	1 (1.3)
Intermediate	114 (34.1)	923 (34.6)	85 (36.0)	521 (37.1)	3070 (32.5)	190 (32.9)	125 (36.5)	558 (33.9)	26 (33.8)
Healthy	207 (62.0)	1707 (64.0)	148 (62.7)	857 (61.0)	6277 (66.4)	385 (66.6)	212 (62.0)	1073 (65.1)	50 (64.9)
Cancer, N (%)[3]	29 (10.1)	239 (10.4)	13 (8.6)	100 (11.0)	728 (10.0)	39 (10.6)	33 (12.6)	182 (11.3)	11 (15.1)

All values represent Mean (SD) unless noted otherwise

[1]1 unit = 8 g of ethanol; [2]sleep patterns were determined based on the method proposed by Fan M. et al (ref 29). In brief, participants were categorized by how many healthy sleep characteristics (morning chronotype, adequate sleep duration (7-8 hr./d), never or rare insomnia, never or rare snoring, and infrequent daytime sleepiness) they displayed into three groups (healthy: ≥ 4; intermediate: 2-3; poor: ≤ 1)

[3]Physician diagnosed (self-reported and cancer registry)

Supplemental Table 2: Sequential covariate adjustments for baseline physical activity, body mass index, body fat percentage, waist to hip ratio, and waist circumference changes with all-cause mortality

A) Physical activity

Baseline	Change	Model 1	Model 2
Inactive			
	Stable	1.04(0.43,2.54)	1.00(0.41,2.42)
	Increased	0.74(0.49,1.12)	0.72(0.47,1.09)
Insufficient			
	Decreased	1.46(0.81,2.63)	1.39(0.77,2.51)
	Stable	Ref.	Ref.
	Increased	0.64(0.49,0.84)	0.64(0.49,0.84)
Sufficient			
	Decreased	1.04(0.8,1.33)	1.00(0.78,1.29)
	Stable	0.75(0.61,0.93)	0.74(0.6,0.91)

B) Body Mass Index

Baseline	Change	Model 1	Model 2
Obese			
	Stable	1.87(1.49,2.35)	1.80(1.43,2.26)
	Decreased	1.02(0.64,1.62)	1(0.63,1.59)
Overweight			
	Decreased	0.63(0.4,1.01)	0.65(0.41,1.03)
	Stable	Ref.	Ref.
	Increased	1.35(0.88,2.07)	1.3(0.85,1.99)
Normal			
	Increased	0.97(0.64,1.45)	0.97(0.64,1.45)
	Stable	1.09(0.88,1.36)	1.14(0.91,1.42)

C) Body Fat

Baseline	Change	Model 1	Model 2
High			
	Stable	1.57 (1.24, 1.99)	1.50 (1.18, 1.89)
	Decreased	0.73 (0.42, 1.27)	0.71 (0.41, 1.23)
Moderate			
	Decreased	1.14 (0.77, 1.68)	1.15 (0.78, 1.70)
	Stable	Ref.	Ref.
	Increased	1.00 (0.71, 1.40)	0.97 (0.69, 1.35)
Low			
	Increased	0.91 (0.66, 1.26)	0.92 (0.66, 1.27)

	Stable	0.89 (0.70, 1.14)	0.92 (0.72, 1.19)

D) Waist to Hip Ratio

Baseline	Change	Model 1	Model 2
High			
	Stable	1.71(1.19,2.45)	1.66(1.15,2.38)
	Decreased	1.64(1.11,2.41)	1.61(1.09,2.37)
Moderate			
	Decreased	1.32(0.89,1.94)	1.33(0.9,1.97)
	Stable	Ref.	Ref.
	Increased	1.54(1.04,2.27)	1.51(1.03,2.24)
Low			
	Increased	0.93(0.65,1.31)	0.93(0.66,1.33)
	Stable	0.80(0.58,1.1)	0.83(0.6,1.14)

E) Waist Circumference

Baseline	Change	Model 1	Model 2
High			
	Stable	1.58 (1.24, 2.05)	1.49 (1.16, 1.94)
	Decreased	1.32 (1.10, 1.89)	1.22 (0.92, 1.80)
Moderate			
	Decreased	0.68 (0.43, 1.03)	0.70 (0.45, 1.05)
	Stable	Ref.	Ref.
	Increased	1.18 (0.82, 1.72)	1.13 (0.77, 1.65)
Low			
	Increased	0.72 (0.49, 1.06)	0.75 (0.52, 1.09)
	Stable	0.74 (0.54, 1.01)	0.77 (0.57, 1.04)

Model 1 (M1) adjusted for age, sex
Model 2 (M2) adjusted for M1 plus smoking status, alcohol consumption, sleep pattern, fruits and vegetables consumption, deprivation index, physical activity baseline and change (or body mass index baseline and change for physical activity as an exposure), and education

Supplemental Table 3: Sequential covariate adjustments for baseline physical activity, body mass index, body fat percentage, waist to hip ratio, and waist circumference changes with cardiovascular disease

A) Physical activity

Baseline	Change	Model 1	Model 2
Inactive			
	Stable	1.44(0.92,2.26)	1.41(0.90,2.21)
	Increased	0.87(0.70,1.07)	0.85(0.69,1.05)
Insufficient			
	Decreased	1.47(1.06,2.04)	1.42(1.02,1.99)
	Stable	Ref.	Ref.
	Increased	0.83(0.72,0.96)	0.83(0.72,0.96)
Sufficient			
	Decreased	1.12(0.97,1.29)	1.10(0.95,1.27)
	Stable	0.90(0.80,1.01)	0.88(0.78,0.99)

B) Body Mass Index

Baseline	Change	Model 1	Model 2
Obese			
	Stable	1.36(1.2,1.55)	1.34(1.18,1.52)
	Decreased	0.71(0.48,1.05)	0.71(0.48,1.05)
Overweight			
	Decreased	0.69(0.54,0.89)	0.70(0.55,0.91)
	Stable	Ref.	Ref.
	Increased	1.15(0.92,1.42)	1.12(0.90,1.39)
Normal			
	Increased	0.89(0.72,1.1)	0.88(0.72,1.09)
	Stable	0.83(0.74,0.93)	0.85(0.76,0.96)

C) Body Fat

Baseline	Change	Model 1	Model 2
High			
	Stable	1.48 (1.30, 1.69)	1.44 (1.27, 1.65)
	Decreased	1.12 (0.83, 1.53)	1.12 (0.82, 1.52)
Moderate			
	Decreased	0.80 (0.61, 1.06)	0.81 (0.61, 1.07)
	Stable	Ref.	Ref.
	Increased	1.18 (1.00, 1.38)	1.15 (0.98, 1.36)
Low			
	Increased	0.89 (0.76, 1.05)	0.89 (0.76, 1.05)
	Stable	0.86 (0.76, 0.98)	0.88 (0.77, 1.00)

D) Waist to Hip Ratio

Baseline	Change	Model 1	Model 2
High			
	Stable	1.06(0.88,1.28)	1.05(0.86,1.27)
	Decreased	1.20(0.97,1.47)	1.19(0.97,1.46)
Moderate			
	Decreased	0.82(0.66,1.01)	0.83(0.67,1.02)
	Stable	Ref.	Ref.
	Increased	0.96(0.78,1.17)	0.95(0.77,1.16)
Low			
	Increased	0.74(0.62,0.88)	0.74(0.62,0.88)
	Stable	0.71(0.61,0.83)	0.72(0.62,0.84)

E) Waist Circumference

Baseline	Change	Model 1	Model 2
High			
	Stable	1.65 (1.45, 1.90)	1.54 (1.34, 1.79)
	Decreased	1.14 (0.92, 1.42)	1.05 (0.83, 1.33)
Moderate			
	Decreased	0.60 (0.35, 0.82)	0.66 (0.41, 0.87)
	Stable	Ref.	Ref.
	Increased	1.19 (1.00, 1.46)	1.15 (0.95, 1.41)
Low			
	Increased	0.71 (0.56, 0.89)	0.77 (0.62, 0.95)
	Stable	0.68 (0.56, 0.81)	0.74 (0.62, 0.88)

Model 1 (M1) adjusted for age, sex
Model 2 (M2) adjusted for M1 plus smoking status, alcohol consumption, sleep pattern, fruits and vegetables consumption, deprivation index physical activity baseline and change (or body mass index baseline and change for physical activity as an exposure), and education

Supplemental Table 4: Separate association of physical activity, body mass index, body fat Percentage, waist circumference, and waist to hip ratio baseline changes with all-cause mortality risk; exclusion of prevalent cancer

Baseline physical activity/adiposity	Change	Physical activity	BMI	Body fat percentage	Waist circumference	Waist to hip ratio
Inactive/ Obese/High						
	Stable	1.55 (1.15, 1.96)	0.96 (0.60, 1.57)	0.73 (0.44, 1.02)	1.20 (0.78, 1.77)	1.58 (1.07, 2.34)
	Increased	0.74 (0.51, 1.13)	1.81 (1.44, 2.30)	1.51 (1.15, 1.92)	1.49 (1.15, 1.95)	1.65 (1.15, 2.38)
Insufficient/ Overweight/Moderate						
	Decreased	1.41 (1.07, 1.91)	0.67 (0.44, 1.04)	0.93 (0.66, 1.38)	0.72 (0.48, 1.14)	1.36 (0.88, 2.02)
	Stable	Reference	Reference	Reference	Reference	Reference
	Increased	0.65 (0.51, 0.88)	1.32 (0.86, 2.01)	1.18 (0.78, 1.75)	1.14 (0.78, 1.67)	1.53 (1.04, 2.26)
Sufficient/ Healthy/Low						
	Decreased	0.99 (0.78, 1.30)	1.08 (0.87, 1.37)	0.92 (0.71, 1.20)	0.80 (0.61, 1.06)	0.85 (0.63, 1.17)
	Stable	0.72 (0.58, 0.89)	0.95 (0.65, 1.45)	0.96 (0.68, 1.32)	0.79 (0.57, 1.13)	0.92 (0.65, 1.33)

Adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, physical activity baseline group, deprivation index. 408 deaths for BMI, waist circumference, and waist to hip ratio (n=26,339) and 392 deaths for body fat percentage (n=25,497)

Supplemental Table 5: Joint association of changes in physical activity and adiposity with all-cause mortality risk; exclusion of prevalent cancer

Physical activity change	Adiposity change	BMI	Body fat percentage	Waist circumference	Waist to hip ratio
Decreased					
	Decreased	0.79 (0.35, 1.93)	0.85 (0.38, 1.49)	0.96 (0.71, 1.23)	1.71 (1.04, 2.82)
	Stable	1.18 (0.88, 1.62)	1.20 (0.90, 1.56)	1.16 (0.93, 1.78)	1.26 (0.92, 1.78)
	Increased	1.22 (0.68, 1.98)	1.25 (0.82, 1.93)	1. 69 (1.06, 2.75)	1.22 (0.78, 1.83)
Stable					
	Decreased	0.74 (0.52, 1.07)	0.82 (0.64, 1.11)	0.84 (0.58, 1.09)	1.52 (1.21, 2.04)
	Stable	Reference	Reference	Reference	Reference
	Increased	0.94 (0.65, 1.35)	1.01 (0.71, 1.46)	1.24 (1.02, 2.36)	1.06 (0.83, 1.41)
Increased					
	Decreased	0.44 (0.20, 0.89)	0.59 (0.28, 0.94)	0.64 (0.43, 0.88)	0.91 (0.52, 1.54)
	Stable	0.78 (0.60, 1.01)	0.75 (0.58, 0.93)	0.83 (0.66, 0.99)	0.78 (0.57, 1.04)
	Increased	0.80 (0.48, 1.02)	0.75 (0.44, 1.29)	1.05 (0.72, 1.53)	1.07 (0.76, 1.59)

Adjusted for age, sex, baseline physical activity group, baseline waist to hip ratio group; smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index. 408 deaths for BMI, waist circumference, and waist to hip ratio (n=26,339) and 392 deaths for body fat percentage (n=25,497)

Supplemental Table 6: E-values for separate association of physical activity, body mass index, and body fat percentage baseline changes with all-cause mortality risk

A) Physical activity	Change	E-value
Inactive		
	Stable	2.4 (1.5)
	Increased	2.2 (1.0)
Insufficient		
	Decreased	2.1 (1.3)
	Stable	-
	Increased	2.5 (1.6)
Sufficient		
	Decreased	1.0 (1.0)
	Stable	2.0 (1.4)

B) Body mass index	Change	E-value
Obese		
	Stable	1.2 (1.0)
	Increased	2.9 (2.1)
Overweight		
	Decreased	2.5 (1.0)
	Stable	-
	Increased	1.9 (1.0)
Healthy		
	Decreased	1.5 (1.0)
	Stable	1.3 (1.0)

C) Body Fat	Change	E-value
High		
	Stable	2.3 (1.2)
	Increased	2.3 (1.6)
Moderate		
	Decreased	1.3 (1.0)
	Stable	-
	Increased	1.6 (1.0)
Low		
	Decreased	1.4 (1.0)
	Stable	1.4 (1.0)

Values represent: E-value (interval bound)

adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, physical activity baseline and change group (or body mass index baseline and change group for physical activity as an exposure), and cancer diagnosis.

Supplemental Table 7: E-values for separate association of physical activity, body mass index, and body fat percentage baseline changes with cardiovascular disease incidence risk

A) Physical activity	Change	E-value
Inactive		
	Stable	2.2 (1.0)
	Increased	1.6 (1.0)
Insufficient		
	Decreased	2.2 (1.2)
	Stable	-
	Increased	1.7 (1.3)
Sufficient		
	Decreased	1.4 (1.0)
	Stable	1.5 (1.1)

B) Body mass index	Change	E-value
Obese		
	Stable	2.2 (1.0)
	Increased	2.0 (1.6)
Overweight		
	Decreased	2.2 (1.4)
	Stable	-
	Increased	1.5 (1.0)
Healthy		
	Decreased	1.6 (1.3)
	Stable	1.5 (1.0)

C) Body Fat	Change	E-value
High		
	Stable	1.5 (1.0)
	Increased	2.3 (1.9)
Moderate		
	Decreased	1.8 (1.0)
	Stable	-
	Increased	1.6 (1.0)

Low		
	Decreased	1.5 (1.0)
	Stable	1.5 (1.0)

Values represent: E-value (interval bound)

adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, physical activity baseline and change group (or body mass index baseline and change group for physical activity as an exposure), and cancer diagnosis.

Supplemental Table 8: E-values for Joint association of changes in physical activity and adiposity with all-cause mortality risk

A) Physical activity	**Body mass index**	**E-value**
Decreased		
	Decreased	1.9 (1.0)
	Stable	1.7 (1.0)
	Increased	1.6 (1.0)
Stable		
	Decreased	2.2 (1.0)
	Stable	-
	Increased	1.4 (1.0)
Increased		
	Decreased	3.7 (1.3)
	Stable	1.8 (1.0)
	Increased	1.8 (1.0)

B) Physical activity	**Body fat**	**E-value**
Decreased		
	Decreased	1.7 (1.0)
	Stable	1.8 (1.0)
	Increased	1.7 (1.0)
Stable		
	Decreased	1.8 (1.0)
	Stable	-
	Increased	1.2 (1.0)
Increased		
	Decreased	2.6 (1.4)
	Stable	1.9 (1.3)
	Increased	2.0 (1.0)

Values represent: E-value (interval bound)

Adjusted for age, sex, baseline physical activity, baseline body mass index (or body fat percentage); smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis.

Supplemental Table 9: E-values for Joint association of changes in physical activity and adiposity with cardiovascular disease incidence risk

A) Physical activity	Body mass index	E-value
Decreased		
	Decreased	1.8 (1.0)
	Stable	1.7 (1.2)
	Increased	1.6 (1.0)
Stable		
	Decreased	2.1 (1.3)
	Stable	-
	Increased	1.3 (1.0)
Increased		
	Decreased	2.5 (1.3)
	Stable	1.5 (1.0)
	Increased	1.3 (1.0

B) Physical activity	Body fat	E-value
Decreased		
	Decreased	1.1 (1.0)
	Stable	1.7 (1.2)
	Increased	1.8 (1.0)
Stable		
	Decreased	1.4 (1.0)
	Stable	-
	Increased	1.3 (1.0)
Increased		
	Decreased	2.0 (1.2)
	Stable	1.5 (1.2)
	Increased	1.6 (1.0)

Values represent: E-value (interval bound)

Adjusted for age, sex, baseline physical activity, baseline body mass index (or body fat percentage); smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplemental Figure 1
		(b) Give reasons for non-participation at each stage	Supplemental Figure 1
		(c) Consider use of a flow diagram	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 and Supplemental Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11, Figures 1-4
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figures 1-4, Supplemental Tables 1-2
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-15 Supplemental Figures 6-7,
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20