Electronic Supplementary Materials

Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants

Ziyi Zhou[1], John Macpherson[1], Stuart R Gray[2], Jason M R Gill[2], Paul Welsh[2], Carlos Celis-Morales[1,2,3], Naveed Sattar[2], Jill P Pell[1], Frederick K Ho[1]

[1]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[3]Human Performance Lab, Education, Physical Activity and Health Research Unit, University Católica del Maule, Talca, Chile

Carlos Celis-Morales, Naveed Sattar, Jill P. Pell and Frederick K. Ho are joint senior authors.

Corresponding author:
Frederick Ho,
Email: Frederick.Ho@glasgow.ac.uk

ESM Table 1. Criteria for metabolically healthy

Biomarker	**Criteria for Metabolically Healthy**
BP	SBP <130 mmHg and DBP <80 mmHg and no antihypertensive medications
C-reactive protein (CRP)	CRP <3 mg/L
Triacylglycerols	Triacylglycerols <2.3 mmol/L
Low-density lipoprotein cholesterol (LDL-c)	LDL-c <3 mmol/L and no cholesterol lowering medications
High-density lipoprotein cholesterol (HDL-c)	HDL-c >1 mmol/L
Glycated haemoglobin	HbA_{1c} <42 mmol/mol (6%) and no diabetes medications

ESM Table 2. Association between MHO and incidence outcomes

	Model 1		Model 2	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Diabetes				
MHN	1 (Reference)		1 (Reference)	
MHO	4.79 (4.27, 5.37)	<0.0001	4.55 (4.05, 5.10)	<0.0001
MUN	5.67 (5.16, 6.22)	<0.0001	5.43 (4.94, 5.96)	<0.0001
MUO	14.79 (13.56, 16.13)	<0.0001	13.72 (12.57, 14.98)	<0.0001
ASCVD				
MHN	1 (Reference)		1 (Reference)	
MHO	1.22 (1.14, 1.30)	<0.0001	1.15 (1.08, 1.23)	<0.0001
MUN	1.68 (1.61, 1.75)	<0.0001	1.62 (1.55, 1.69)	<0.0001
MUO	1.90 (1.82, 1.99)	<0.0001	1.77 (1.69, 1.85)	<0.0001
MI				
MHN	1 (Reference)		1 (Reference)	
MHO	1.26 (1.14, 1.39)	<0.0001	1.20 (1.09, 1.32)	0.0003
MUN	1.93 (1.82, 2.05)	<0.0001	1.87 (1.76, 1.98)	<0.0001
MUO	2.14 (2.00, 2.28)	<0.0001	1.99 (1.87, 2.13)	<0.0001
Stroke				
MHN	1 (Reference)		1 (Reference)	
MHO	1.12 (1.03, 1.22)	0.01	1.07 (0.98, 1.17)	0.12
MUN	1.32 (1.25, 1.39)	<0.0001	1.28 (1.21, 1.36)	<0.0001
MUO	1.48 (1.39, 1.57)	<0.0001	1.40 (1.31, 1.49)	<0.0001
HF				
MHN	1 (Reference)		1 (Reference)	
MHO	1.93 (1.78, 2.10)	<0.0001	1.81 (1.67, 1.96)	<0.0001
MUN	1.55 (1.46, 1.65)	<0.0001	1.49 (1.40, 1.58)	<0.0001
MUO	2.93 (2.76, 3.11)	<0.0001	2.68 (2.52, 2.84)	<0.0001
Respiratory disease				
MHN	1 (Reference)		1 (Reference)	
MHO	1.37 (1.33, 1.41)	<0.0001	1.30 (1.26, 1.35)	<0.0001
MUN	1.32 (1.29, 1.35)	<0.0001	1.27 (1.24, 1.30)	<0.0001
MUO	1.65 (1.61, 1.68)	<0.0001	1.53 (1.49, 1.57)	<0.0001
COPD				
MHN	1 (Reference)		1 (Reference)	
MHO	1.41 (1.31, 1.51)	<0.0001	1.18 (1.10, 1.27)	<0.0001
MUN	1.82 (1.74, 1.90)	<0.0001	1.62 (1.55, 1.70)	<0.0001
MUO	2.24 (2.13, 2.35)	<0.0001	1.74 (1.66, 1.83)	<0.0001

Model 1: Adjusted for age, sex, and ethnicity only.
Model 2: Additionally adjusted for education level and deprivation index.
MHN: metabolically healthy non-obese; MHO; metabolically healthy obese; MUN; metabolically unhealthy non-obese; MUO metabolically unhealthy obese

ESM Table 3. Association between MHO and mortality outcomes

	Model 1		Model 2	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
All-cause mortality				
MHN	1 (Reference)		1 (Reference)	
MHO	1.27 (1.19, 1.36)	< 0.0001	1.21 (1.13, 1.29)	< 0.0001
MUN	1.38 (1.33, 1.44)	< 0.0001	1.34 (1.28, 1.40)	< 0.0001
MUO	1.69 (1.62, 1.77)	< 0.0001	1.57 (1.49, 1.64)	< 0.0001
ASCVD				
MHN	1 (Reference)		1 (Reference)	
MHO	1.47 (1.28, 1.68)	< 0.0001	1.36 (1.18, 1.56)	< 0.0001
MUN	1.96 (1.80, 2.14)	< 0.0001	1.87 (1.72, 2.04)	< 0.0001
MUO	2.50 (2.29, 2.74)	< 0.0001	2.23 (2.04, 2.45)	< 0.0001
MI				
MHN	1 (Reference)		1 (Reference)	
MHO	1.76 (1.34, 2.33)	< 0.0001	1.63 (1.23, 2.15)	0.0006
MUN	2.53 (2.12, 3.02)	< 0.0001	2.41 (2.02, 2.88)	< 0.0001
MUO	3.08 (2.55, 3.71)	< 0.0001	2.74 (2.27, 3.32)	< 0.0001
Stroke				
MHN	1 (Reference)		1 (Reference)	
MHO	1.13 (0.90, 1.43)	0.30	1.06 (0.84, 1.34)	0.63
MUN	1.32 (1.14, 1.53)	0.0003	1.27 (1.09, 1.47)	0.002
MUO	1.59 (1.36, 1.87)	< 0.0001	1.45 (1.23, 1.71)	< 0.0001
HF				
MHN	1 (Reference)		1 (Reference)	
MHO	2.11 (1.65, 2.70)	< 0.0001	1.92 (1.50, 2.46)	< 0.0001
MUN	2.01 (1.68, 2.40)	< 0.0001	1.90 (1.59, 2.27)	< 0.0001
MUO	3.40 (2.85, 4.05)	< 0.0001	2.97 (2.49, 3.55)	< 0.0001
Respiratory disease				
MHN	1 (Reference)		1 (Reference)	
MHO	1.40 (1.23, 1.60)	< 0.0001	1.24 (1.09, 1.42)	0.002
MUN	1.72 (1.57, 1.87)	< 0.0001	1.60 (1.46, 1.74)	< 0.0001
MUO	2.38 (2.18, 2.60)	< 0.0001	2.00 (1.83, 2.19)	< 0.0001
COPD				
MHN	1 (Reference)		1 (Reference)	
MHO	1.09 (0.83, 1.44)	0.53	0.86 (0.65, 1.13)	0.27
MUN	1.96 (1.68, 2.29)	< 0.0001	1.68 (1.44, 1.97)	< 0.0001
MUO	2.71 (2.31, 3.18)	< 0.0001	1.92 (1.63, 2.26)	< 0.0001

Model 1: Adjusted for age, sex, and ethnicity only.
Model 2: Additionally adjusted for education level and deprivation index.
MHN: metabolically healthy non-obese; MHO; metabolically healthy obese; MUN; metabolically unhealthy non-obese; MUO metabolically unhealthy obese

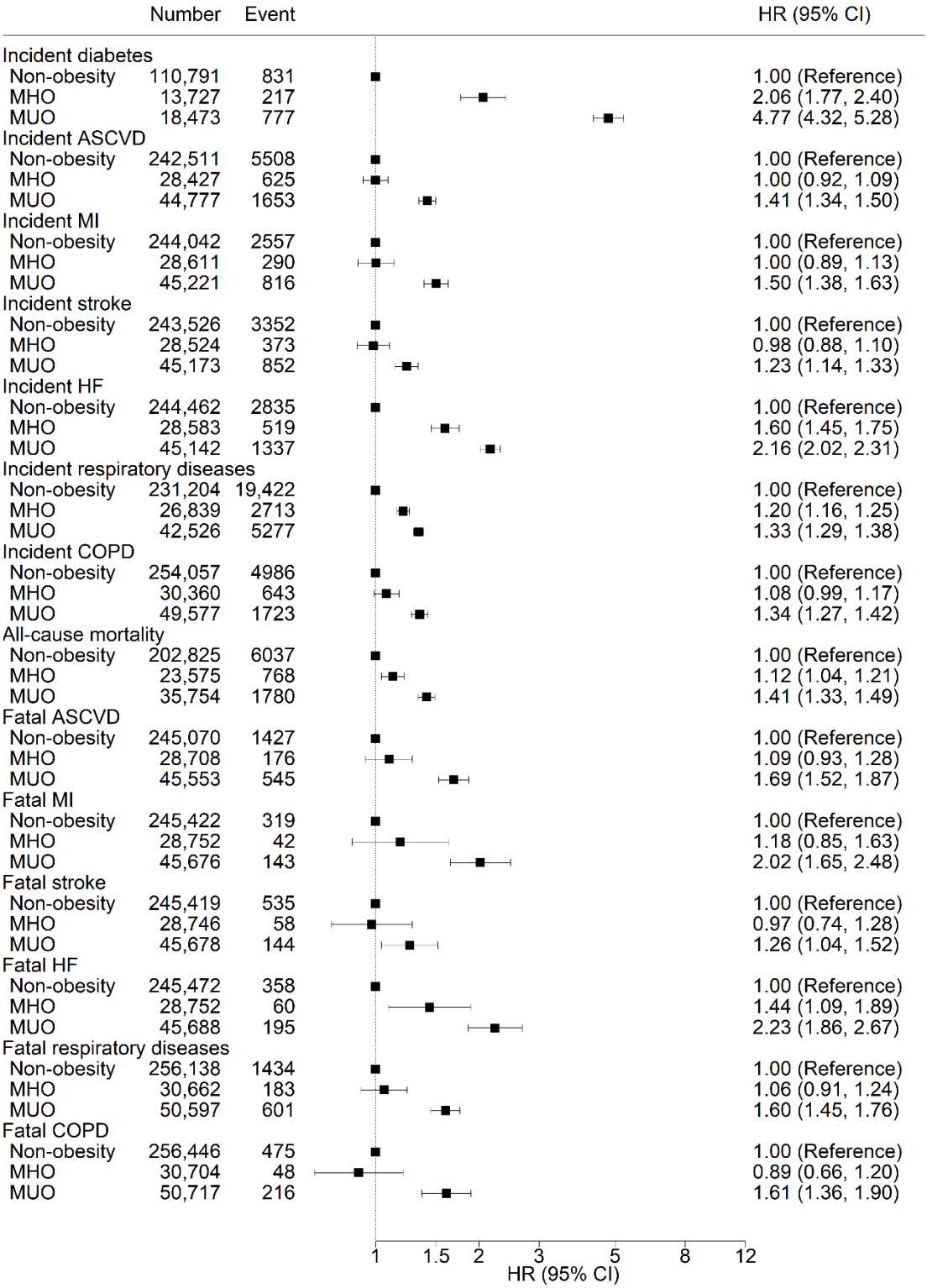
ESM Table 4. Association between incident diabetes and subsequent outcomes with adjustment of baseline MHO status

	HR (95% CI)	P
Incident ASCVD	0.68 (0.59, 0.80)	<0.0001
Incident HF	1.00 (0.86, 1.17)	0.97
All-cause mortality	0.88 (0.79, 0.99)	0.03
Fatal ASCVD	0.83 (0.66, 1.06)	0.14
Fatal HF	1.29 (0.89, 1.87)	0.18

Adjusted for age, sex ethnicity, education, deprivation, smoking, alcohol drinking, television viewing, physical activity, intake of fruit and vegetables, oily fish, red meat and processed meat, and baseline MHO status

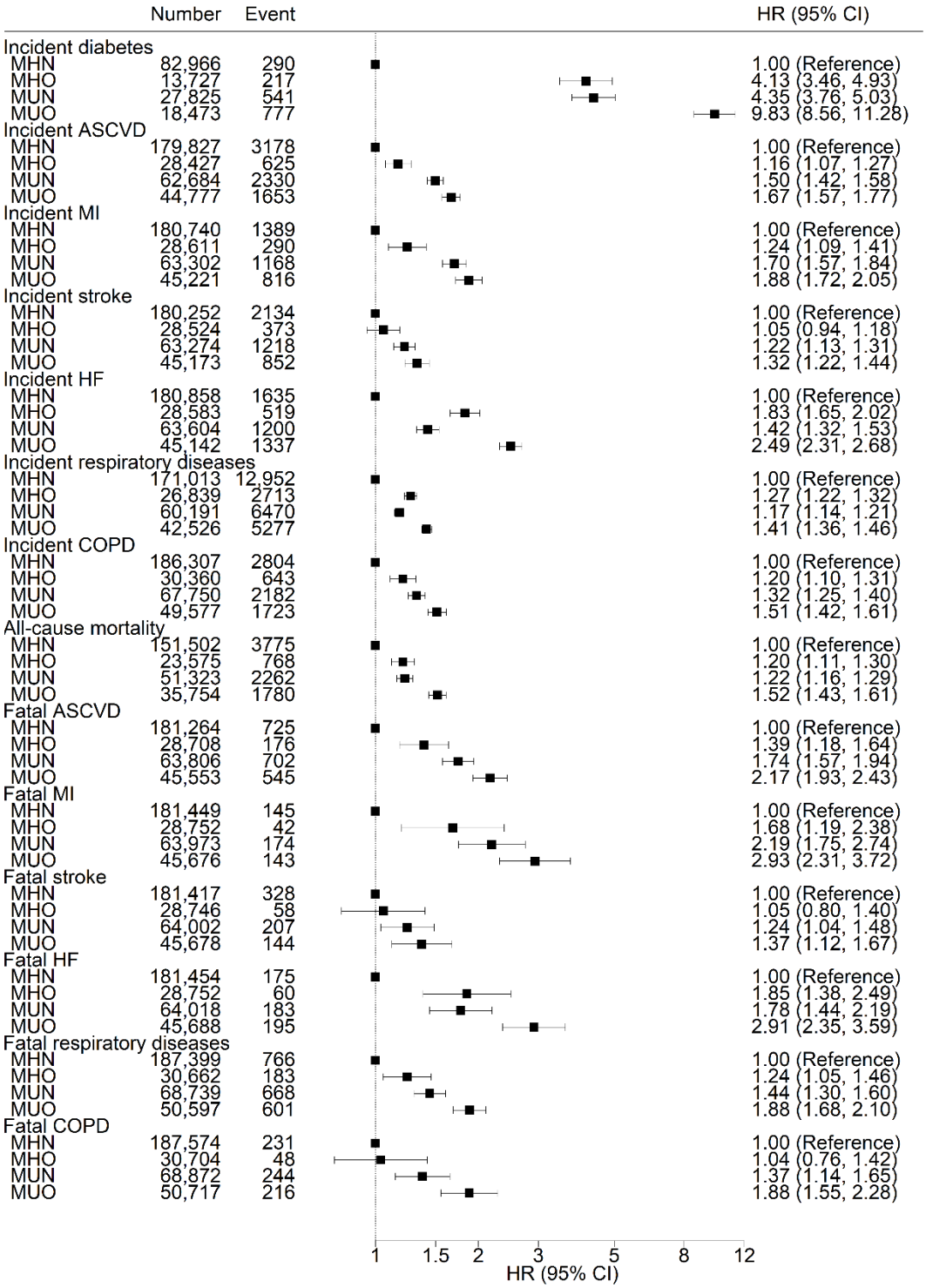
Incident diabetes was the exposure variable coded as 1 when diabetes was recorded between the baseline assessment and the incidence of the outcome (for people who developed the outcome) or the date of censoring (for censored observations), or 0 otherwise.

ESM Figure 1. Association between MHO and health outcomes with non-obesity as reference group



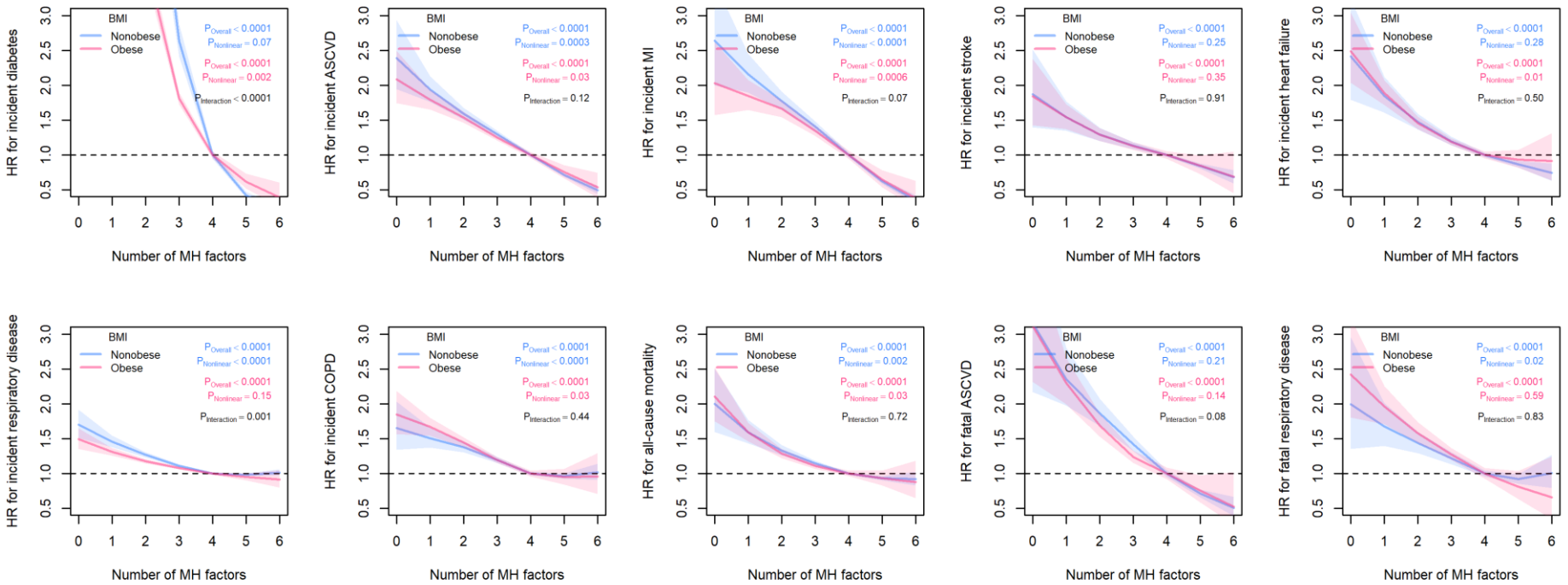
Adjusted for age, sex ethnicity, education, deprivation, smoking, alcohol drinking, television viewing, physical activity, and intake of fruit and vegetables, oily fish, red meat and processed meat
HR shown in logarithmic scale.

ESM Figure 2. Association between MHO and health outcomes in a 5-year landmark analysis



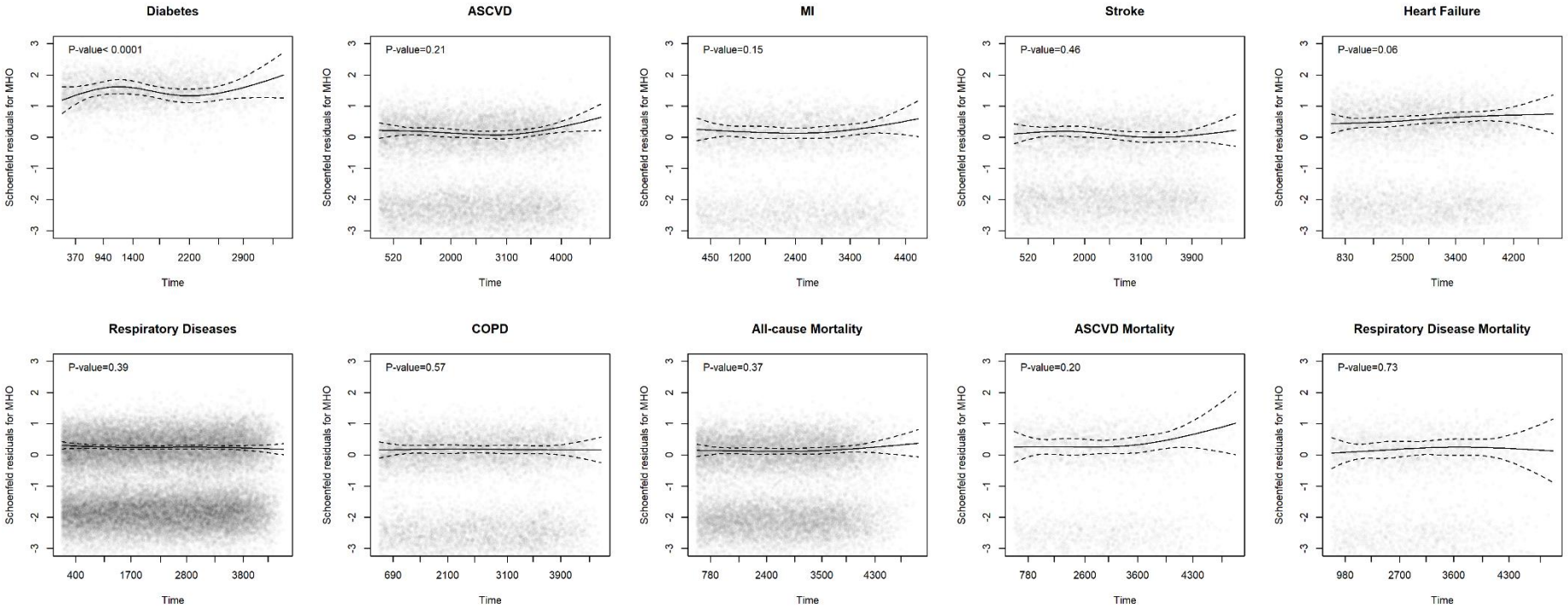
Participants who had corresponding events in the first five years of follow-up were excluded.
Adjusted for age, sex ethnicity, education, deprivation, smoking, alcohol drinking, television viewing, physical activity, and intake of fruit and vegetables, oily fish, red meat and processed meat
HR shown in logarithmic scale.

ESM Figure 3. Interaction of obesity and metabolic health with health outcomes



Main effects of obesity were not shown. Adjusted for each other and for age, sex ethnicity, education, deprivation, smoking, alcohol drinking, television viewing, physical activity, and intake of fruit and vegetables, oily fish, red meat and processed meat.

ESM Figure 4. Schoenfeld residuals for MHO



ESM Figure 5. Transition of metabolic health and obesity status