Does metabolic health in overweight and obesity persist? – Individual variation and cardiovascular mortality over two decades

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Abstract

Objective: Overweight and obese individuals may be metabolically healthy, but attention needs to be given to long-term persistence of this trait and any associated variation in cardiovascular risk.

Design: Cross-sectional and longitudinal variation in metabolic health and associated cardiovascular mortality were analysed in 1099 white European-origin normal-weight and overweight or obese males followed for 20 years.

Methods: Definitions of metabolic health were based on LDL and HDL cholesterol, triglycerides, blood pressure, fasting glucose and cardiovascular risk. Insulin resistance (e.g. HOMA-IR) and sub-clinical inflammation (ESR and white blood cell count) were explored. Cardiovascular mortality risks and persistence of metabolic health status were evaluated.

Results: There were 87 cardiovascular deaths. Insulin resistance was increased in metabolically healthy overweight or obese participants (median HOMA-IR 2.63, 95% CI: 1.79–3.65, $P < 0.001$) relative to normal-weight participants (median HOMA-IR 1.67, 95% CI: 1.08–2.67, $P < 0.001$) as was sub-clinical inflammation but metabolically healthy overweight or obese individuals were not at increased risk of cardiovascular mortality compared with the metabolically healthy normal-weight individuals (hazard ratio 1.13, 95% CI: 0.34–3.72, $P = 0.8$). The proportions of initially metabolically healthy overweight or obese who remained metabolically healthy for visits 2, 3 and 4 were 54, 48 and 39% respectively, and for initially normal-weight individuals, 68, 51 and 41%. A lower proportion of metabolically healthy overweight or obese individuals remained metabolically healthy at visit 2 compared with normal-weight individuals ($P = 0.007$), but proportions converged thereafter.

Conclusions: Despite being insulin resistant and having greater sub-clinical inflammation, and despite instability in metabolic health status, metabolically healthy overweight or obese individuals were at no greater risk of cardiovascular mortality than their normal-weight equivalents.

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Introduction

Overweight (OW) and obesity (OB) are associated with physiologic and metabolic disturbances that predispose towards the development of type 2 diabetes mellitus, cardiovascular disease (CVD) and cancer. In the 1980s, sub-groups of OB individuals were identified that appeared free of typical adiposity-related disturbances

(1), and it was suggested that some OB individuals might not be at increased risk (2). Subsequently, the concept of metabolically healthy (MH) obesity was adopted (3). Estimates of the prevalence of MH OB in Europe range between 2 and 19% in men and 7 and 28% in women (4).

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Problems consistently raised in commentaries on MH OW and OB have included the lack of an agreed definition of metabolic health and the fact that a continuum of variation in metabolic disturbance extends across all levels of adiposity (5, 6, 7, 8). Nevertheless, if a pragmatic definition of MH could be agreed, it might yet be used to identify OW or OB individuals who need not benefit from intensive weight loss. In a detailed review, Stefan *et al.* distinguished three types of investigation, differing according to whether MHO had been defined with reference to insulin sensitivity, cardiorespiratory fitness or a putative 'metabolic syndrome' (7). Measures of insulin sensitivity and cardiorespiratory fitness (and inflammatory markers, which have also been used to define MH) are not routinely available. However, defining MH with reference to readily available risk factor measures does offer a practical tool with which low-risk OW or OB individuals might be identified.

In the present analysis, we explore data from the HDDRISC study, in which a broad range of risk factors was recorded in 1191 white European males, a substantial proportion of whom had repeated follow-up information recorded at 2–3-year intervals. Applying a definition of MH based on readily available risk factor measurements and their associated CVD mortality risks in the HDDRISC cohort, we test the following hypotheses: (i) MH overweight or obese (OWOB) individuals are at greater risk of CVD mortality than MH normal-weight (NW) individuals; (ii) MH OWOB individuals are insulin resistant and exhibit sub-clinical inflammation relative to MH NW individuals and (iii) MH in OWOB individuals is a persistent trait, sustained over long-term follow-up.

Subjects and methods

Design

The Heart Disease and Diabetes Risk Indicators in a Screened Cohort (HDDRISC) study began as a company health program to evaluate risk factors for CVD and diabetes. The study recruited 1191 white European males (age range 25–70 years; BMI range 18.1–46.9 kg/m²) who were generally healthy and either in employment or recently retired and data acquisition was between June 1971 and January 2000. Metabolic, clinical and laboratory measurements were recorded for each participant at their first visit, and for those continuing in the study, at subsequent follow-up visits every 2–3 years. Ethics committee approval was obtained and each participant gave written, informed consent.

Procedures

Procedures have been described in detail previously (9). Briefly, participants were instructed to fast overnight and, before attendance at a metabolic day ward the next morning, refrain from drinking alcohol and smoking. Demographic data, including self-reported cigarette smoking (0, <15, ≥15 cigarettes per day), alcohol consumption (0, <28, ≥28 units per week) and exercise habits (none, nonaerobic, aerobic, with aerobic distinguished as 3 or more periods of ≥20 min of exercise to breathlessness) and medical history were recorded. After 15 min in a semi-recumbent position, systolic and diastolic blood pressures (SBP and DBP respectively) were measured. Blood samples were taken from an indwelling cannula for laboratory measurements. A further sample was taken 5–10 min later for a second measurement of fasting plasma glucose and insulin (FPG and FPI). The majority of participants then underwent an oral glucose tolerance test (OGTT: 50% dextrose solution at 1 g glucose/kg body weight) and samples were taken to measure plasma glucose and insulin at 30, 60, 90, 120, 150 and 180 min.

Laboratory measurements

Plasma glucose and insulin and serum triglycerides and total, HDL and LDL cholesterol concentrations were measured by the HDDRISC research group as described previously (9). Routine haematology and biochemistry measurements included white blood cell count (WBC) and erythrocyte sedimentation rate (ESR) as indices of sub-clinical inflammation and were undertaken either by the research group or the local chemical pathology laboratory. Between- and within-batch quality control was monitored by frozen, pooled plasma samples and commercially obtained lyophilised sera and by participation in relevant national quality assurance schemes with particular attention paid to long-term assay standardisation.

Definition of metabolic health

Clearly, increased BMI cannot be included as a criterion for MH in an analysis of MH OW or OB, and this extends to increased waist circumference which displays marked co-linearity with BMI (4) and has been excluded from the majority of definitions of MH OW or OB (7, 10, 11, 12). Other readily available criteria then include plasma lipid, lipoprotein and glucose concentrations and blood pressure. Five criteria are considered in the present analysis: LDL-C of ≥3.36 mmol/L or use of a statin and

(with cut-offs defined according to metabolic syndrome criteria (13, 14)) TG ≥ 1.7 mmol/L or use of a fibrate, HDL-C < 1.03 mmol/L, SBP ≥ 130 mmHg systolic or DBP ≥ 85 mmHg or use of blood pressure-lowering agents and FPG ≥ 5.6 mmol/L or a diagnosis of diabetes mellitus and/or use of glucose-lowering agents. The question then arises, how many, if any, of the criteria may be allowed to be present before MH can be excluded? Previous studies of MHO employing similar criteria have allowed none (4, 12, 15), ≤ 1 (10, 11, 16, 17) or ≤ 2 (18, 19, 20, 21). In the present analysis, in the full dataset before exclusions (see below), each of the five risk factors was confirmed as a predictor of CVD and total mortality in univariate Cox proportional hazards models, unadjusted for any factors that might influence variation in risk factor levels. Participants were then distinguished according to whether they had 0, 1, 2, 3, 4 or 5 risk factors and numbers of risk factors were entered as dummy variables in an unadjusted Cox model to determine at what level of risk factor number significant risk of CVD or total mortality would become apparent. Participants with fewer than that number were then identified as MH – ‘metabolically healthy’ – and those with that number or more as MUH – ‘metabolically unhealthy’. We, therefore, ‘calibrated’ our criteria for MH against actual clinical risks they conferred in the HDDRISC cohort.

Definition of overweight

Preliminary analysis indicated that among obese (BMI ≥ 30.0 kg/m²) participants, numbers were insufficient for a reliable evaluation of CVD mortality (12 CVD deaths among the 83 OB participants, with only 1 CVD death (5 deaths in total) among the 13 MH OB participants). Therefore, OW and OB individuals were combined in a single group (OWOB). Rather than the conventional lower limit for OW of 25.0 kg/m², we adopted a limit of 27.0 kg/m² to enable a meaningful evaluation of the relative benefits or otherwise of MH in overweight individuals: with a lower limit of BMI of ≥ 25.0 kg/m², the Cox model hazard ratio for OWOB as a predictor of CVD mortality (101 CVD deaths before exclusions) was 1.32, 95% CI: 0.90–1.94, $P=0.1$, whereas with a lower limit of BMI of ≥ 27.0 kg/m², the hazard ratio was 1.95, 95% CI: 1.33–2.87, $P=0.001$. A lower limit of 27 kg/m² therefore provided for an appreciably higher risk background against which to distinguish whether MH OWOB individuals were or were not at increased risk relative to MH NW individuals.

Cardiovascular disease and total mortality ascertainment

Deaths in the UK were identified through the NHS Information Centre for Health and Social Care. Deaths overseas were notified by family members of the deceased and by the company for which the health screening programme was undertaken. Mortality information was complete to 1 January 2014, with the exception of 27 individuals who are no longer traceable. Fifteen of the 27 who were lost to mortality follow-up were also lost to any further clinical follow-up after their first study visit and therefore had zero follow-up time. Mean mortality follow-up time in the remaining 1176 was 25.7 years (range 0.5–42.5 years).

Death from CVD was assigned if myocardial infarction, coronary artery disease or thrombosis, cerebrovascular incident, stroke, peripheral vascular disease or aortic aneurysm (ICD-10 codes I20–I25; I63–I67 and I70–I73) was recorded as a primary cause of death.

Statistical analysis

Participants with pre-existing CVD or incomplete data for BMI, blood pressure, triglycerides, HDL-C, FPG and LDL-C were excluded. FPG and FPI concentrations were calculated as the mean of the two fasting measurements. The homeostasis model assessment index of insulin resistance (HOMA-IR) (22) and the Matsuda index of insulin sensitivity (Matsuda-SI) (23) were calculated.

Statistical analyses were carried out using StataCorp. 2013 (*Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP). Risks of CVD and total mortality in MH or MUH OWOB participants relative to their NW equivalents were evaluated by Cox proportional hazards modelling with adjustment for age, smoking, alcohol and exercise (as categorised above) to diminish any confounding effect these covariates might have on relationships between adiposity, metabolic health and CVD mortality risk. Primary analyses concerned relationships between baseline characteristics and CVD and total mortality risks. Secondary analyses included follow-up information, with OWOB and confounding variables treated as discrete, time-varying covariates. Kruskal–Wallis analysis of variance, the Mann–Whitney test and the proportions test were applied as appropriate. The number of participants decreased with increasing number of follow-up visits. Therefore, analyses were undertaken for visits 1–2 in the sub-group of individuals

with 2 or more visits, for visits 1–3 in the sub-group of individuals with 3 or more visits, through to visits 1–10 in the sub-group of individuals with 10 or more visits. In this way, numbers of observations at each visit within each number-of-visits sub-group were the same. Risk of transition from MH to MUH was evaluated by Cox proportional hazards modelling in three models according to the 'naïve' and 'longitudinal' approaches distinguished by Twisk *et al.* (24). In Model 1, time to first occurrence of MUH in those MH at baseline was predicted by baseline OWOB status and covariates. In Models 2 and 3, MUH was treated as a recurrent event in the full dataset and predicted, according to the Andersen–Gill model (25), by OWOB status and covariates either at baseline (Model 2) or as discrete, time-varying covariates (Model 3).

Results

Characteristics at first visit for the 1191 participants in the cohort are summarised in Table 1. Exclusions due to existing CVD or missing metabolic health variables are summarised in Supplementary Fig. 1 (see section on supplementary data given at the end of this article). After exclusions, there were 1099 participants with a first visit with complete data for BMI, LDL-C, TG, HDL-C, blood pressure and FPG. Median age was 46.6 years, (range 25–70 years) and median BMI 25.6 kg/m² (range 18.1–46.9 kg/m²). Sixty-nine percent were non-smokers; 65% consumed <28 units/week of alcohol; 40% took no exercise and 41% undertook nonaerobic exercise. Prescription drug use at baseline was limited: 5 on glucose-lowering agents, 3 on statins, 1 on a fibrate and 20 on blood pressure-lowering agents. Of the 1099 participants, 955 had a measurement of FPG as well as FPG and 631 had an OGTT with measures of plasma glucose and insulin.

Criteria for metabolic health

After exclusions, there were 87 CVD deaths during a mean follow-up time of 24.6 years (range 0.5–42.5 years, excluding nine participants lost to mortality follow-up and with no clinical follow-up). In univariate Cox proportional hazards modelling, each of the five defining risk factors for MH was a significant predictor of CVD and of total mortality (Supplementary Table 1). Nevertheless, in the presence of only a single risk factor of any type, risks of CVD and total mortality (unadjusted for factors contributing to risk factor variation) were not significantly raised (hazard ratio (HR) CVD mortality 1.66, 95% CI:

Table 1 Cohort characteristics.

	No. observations	Median (IQR)/% (n)
Age (year)	1191	46.4 (39.9–51.8)
BMI (kg/m ²)	1182	25.6 (23.7–27.4)
BMI ≥27.0 kg/m ² % (n)	1182	30 (350)
Fasting plasma glucose (mmol/L)	1177	5.3 (5.0–5.6)
Fasting plasma insulin (mU/L)*	1030	9.5 (6.0–14.5)
SBP (mmHg)	1190	123 (115–135)
DBP (mmHg)	1190	80 (70–85)
Total cholesterol	1181	5.36 (4.71–6.11)
Triglycerides (mmol/L)	1181	1.22 (0.86–1.74)
HDL cholesterol (mmol/L)	1004	1.25 (1.08–1.43)
LDL cholesterol (mmol/L)	1003	3.50 (2.86–4.14)
Uric acid (μmol/L)	1163	380 (326–430)
HOMA-IR	1030	2.19 (1.36–3.41)
Matsuda-IS	699	4.71 (3.07–7.17)
White cell count (×10 ⁹)	699	4.71 (3.07–7.17)
ESR	949	5.6 (4.7–6.8)
Family history of diabetes % (n)	1181	35 (411)
Family history of heart disease % (n)	1181	8 (93)
Existing diabetes % (n)	1171	5 (57)
Smoking % (n)	1184	
Non-smoker		67 (797)
<15 Cigarettes/day		20 (241)
≥15 Cigarettes/day		12 (146)
Alcohol % (n)	1179	
<28 U/week		64 (753)
≥28 U/week		36 (426)
Exercise % (n)	1126	
No exercise		41 (460)
Nonaerobic		41 (457)
Aerobic		18 (209)
Current drug use % (n)		
Glucose lowering	1191	0.3 (4)
Lipid lowering	1191	
Statin		0.3 (4)
Fibrate		0.3 (3)
Blood pressure lowering	1191	2.2 (26)
Uric acid lowering	1191	1.0 (12)
Mortality		
Total mortality % (n)	1164	29 (340)
CVD mortality % (n)	1164	10 (111)
Mortality follow-up time (years)	1176	24.8 (18.6–32.9)

0.62–4.48, $P=0.3$; total mortality 1.51, 95% CI: 0.95–2.40, $P=0.08$). With two risk factors, however, the hazard ratio became significant (HR CVD mortality 2.79, 95% CI: 1.07–7.27, $P=0.03$; total mortality 2.07, 95% CI: 1.31–3.28, $P=0.002$). Therefore, our definition of MH allowed for ≤1 of the five risk factors considered. Fifty-four percent of NW and 28% of OWOB individuals were identified as MH (Table 2). MH OWOB participants tended to smoke and drink more than MH NW. Despite being classified as MH according to the specified cut-offs, MH OWOB

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Table 2 Characteristics of individuals metabolically healthy (MH) or metabolically unhealthy (MUH) among normal-weight (NW) and overweight or obese (OWOB) participants. Median (IQR) for continuous variables, percentage (n) for categorical variables. Significant differences between NW and OWOB in MH and MUH groups are shown.

	MH			MUH		
	NW (n=425)	OWOB (n=90)	P	NW (n=358)	OWOB (n=226)	P
Age (years)	44.4 (37.6–49.7)	45.4 (39.7–52.0)	0.09	46.9 (42.3–53.4)	48.0 (42.5–53.8)	0.7
BMI (kg/m ²)	24.2 (22.5–25.4)	28.2 (27.8–29.3)	<0.001	24.8 (23.8–26.0)	28.7 (27.7–30.6)	<0.001
Fasting plasma glucose (mmol/L)	5.1 (4.9–5.3)	5.3 (5.0–5.5)	0.001	5.4 (5.1–5.8)	5.5 (5.2–5.9)	0.1
Fasting plasma insulin (mmol/L)	7.5 (5.0–11.5)	11.0 (7.5–15.5)	<0.001	9.2 (6.0–14.5)	13.0 (9.5–18.5)	<0.001
SBP (mmHg)	120 (110–124)	120 (110–130)	0.004	130 (120–140)	130 (120–140)	0.3
DBP (mmHg)	70 (70–80)	80 (70–84)	<0.001	80 (75–90)	85 (80–90)	0.004
Total cholesterol	4.9 (4.4–5.4)	4.8 (4.4–5.4)	0.5	5.9 (5.3–6.4)	5.8 (5.2–6.6)	0.7
Triglycerides (mmol/L)	0.96 (0.72–1.23)	1.11 (0.76–1.46)	0.007	1.45 (1.04–1.98)	1.78 (1.31–2.55)	<0.001
HDL cholesterol (mmol/L)	1.38 (1.20–1.55)	1.26 (1.14–1.43)	0.002	1.22 (1.04–1.40)	1.12 (0.96–1.27)	<0.001
LDL cholesterol (mmol/L)	3.01 (2.55–3.59)	2.95 (2.60–3.32)	0.6	3.89 (3.43–4.40)	3.72 (3.27–4.32)	0.1
Uric acid (μmol/L)	350 (304–400)	386 (340–449)	<0.001	380 (330–420)	410 (359–460)	<0.001
HOMA-IR	1.67 (1.08–2.67)	2.63 (1.79–3.65)	<0.001	2.27 (1.41–3.47)	3.29 (2.26–4.68)	<0.001
Matsuda-IS	6.03 (4.29–8.24)	3.87 (2.84–4.78)	<0.001	4.37 (3.04–6.66)	2.70 (1.90–4.23)	<0.001
White cell count (×10 ⁹)	5.2 (4.5–6.3)	6.1 (5.2–7.0)	<0.001	5.7 (4.8–7.1)	5.8 (5.0–6.9)	0.2
ESR	3 (2–6)	4 (2–6)	0.08	5 (2–8)	5 (2–10)	0.4
FH heart disease, 1° relative % (n)	33 (141)	26 (23)	0.3	38 (135)	37 (83)	0.2
FH diabetes, 1° relative % (n)	8 (32)	8 (7)	0.9	8 (29)	8 (17)	0.8
Diabetes % (n)	1 (5)	1 (1)	0.9	5 (19)	5 (12)	0.9
Smoking % (n)			0.009			0.3
Non-smoker	74 (313)	60 (53)		65 (231)	71 (159)	
<15 Cigarettes/day	16 (67)	29 (26)		22 (78)	18 (40)	
≥15 Cigarettes/day	10 (44)	11 (10)		13 (46)	12 (26)	
Alcohol % (n)			0.002			0.8
<28 U/week	75 (314)	59 (53)		59 (209)	58 (132)	
≥28 U/week	25 (106)	41 (37)		41 (145)	42 (94)	
Exercise % (n)			0.2			0.1
No exercise	34 (138)	36 (31)		41 (138)	50 (111)	
Nonaerobic	43 (173)	49 (43)		41 (137)	36 (79)	
Aerobic	23 (95)	15 (13)		18 (59)	14 (32)	
Current drug use % (n)						
Glucose lowering	0 (0)	1 (1)	0.03	0.9 (3)	0.4 (1)	0.5
Statin	0 (0)	0 (0)	1.0	0.3 (1)	0.9 (2)	0.3
Fibrate	0 (0)	0 (0)	1.0	0 (0)	0.4 (1)	0.2
Blood pressure lowering	0.5 (2)	1.1 (1)	0.4	2.2 (8)	4.0 (9)	0.2
Mortality						
Total mortality % (n)	18 (77)	23 (21)	0.2	34 (122)	31 (71)	0.5
CVD mortality % (n)	5 (21)	2 (2)	0.2	10 (35)	13 (29)	0.2
Mortality follow-up time (years)	24.9 (18.7–32.9)	22.3 (17.4–29.5)	0.008	25.4 (18.5–32.4)	22.5 (17.4–28.7)	0.002

participants tended to have higher FPG, blood pressure, triglycerides and uric acid and lower HDL cholesterol than MH NW and similar differentials were apparent between MUH OWOB and MUH NW participants. Among OWOB participants, those who were MH were slightly younger and took more exercise than the MUH, but tended to smoke more and have higher alcohol intake.

HOMA-IR and 56% higher according to Matsuda-IS (Table 2). Similar differentials were also seen between MUH OWOB and NW participants. White cell count was also significantly increased in MH OWOB participants compared with MH NW, but this difference was not apparent in MUH participants. ESR showed relatively minor variation, however.

Insulin sensitivity and sub-clinical inflammation in metabolically healthy NW and OWOB

MH OWOB participants had markedly higher insulin resistance than MH NW, 57% higher according to

Metabolic health and CVD and total mortality in NW and OWOB

Independently of age, smoking, alcohol intake and exercise habit, OWOB was a significant predictor of

both CVD (HR 1.76, 95% CI: 1.26–2.44, $P=0.001$) and total (HR 1.38, 95% CI: 1.13–1.67, $P=0.001$) mortality. However, among those who were MH, OWOB ceased to be an independent predictor of CVD mortality (HR 1.13, 95% CI: 0.34–3.72, $P=0.8$). An effect on total mortality was, nevertheless, still apparent (HR 1.60, 95% CI: 1.04–2.47, $P=0.03$). In the full dataset (3129 observations), with OWOB and confounding factors treated as discrete, time-varying covariates, OWOB was again a significant, independent predictor of both CVD (HR 2.02, 95% CI: 1.27–3.21, $P=0.003$) and total (HR 1.55, 95% CI: 1.20–2.01, $P=0.001$) mortality. Among those who were MH at baseline, however, OWOB was a risk factor for neither CVD (HR 0.64, 95% CI: 0.15–2.83, $P=0.5$) nor total (HR 1.38, 95% CI: 0.83–2.90, $P=0.2$) mortality. In contrast to those who were MH, among participants who were MUH at baseline, OWOB remained an independent predictor of mortality with hazard ratios of 1.67 (95% CI: 1.17–2.39, $P=0.004$) and 1.26 (95% CI: 1.01–1.57, $P=0.03$) for CVD and total mortality respectively, and these risks were equally apparent when the full dataset with covariate follow-up was considered.

Prevalence of MH during follow-up

Of the 1099 participants included in this analysis, 608 had a second visit, 404 a third down to 32 with 10 visits. Mean follow-up time between visits 1 and 2 was 3.7 years and ranged between subsequent visits from 2.1 to 2.7 years. Of the 316 participants who were OWOB at their first visit, 160 had one subsequent visit, 96 two subsequent visits to 9 with 10 subsequent visits.

Baseline prevalence of MH was 54% among the 783 NW participants and 28% among the 316 OWOB participants (Supplementary Table 3). In the sub-group of 32 participants who returned for 10 or more visits, the baseline prevalence of MH was 39% in NW and 44% in OBOW individuals and at visit 10, 33% and 38%. In OWOB individuals, there was a trend towards increased prevalence of MH from visits 1–3 (average prevalences across number-of-visits sub-groups, weighted by numbers of observations in each sub-group, were 30, 35 and 43% for visits 1–3 respectively), with an irregular decline in prevalence thereafter. Among individuals OWOB at baseline, baseline prevalences of MH in individuals in number-of-visits sub-groups 1–10 were 28, 26, 31, 35, 33, 35, 38, 34, 41 and 44% respectively, indicating that those who subsequently returned for increasing numbers of follow-up visits had an increased prevalence of MH from the outset.

Table 3 Proportions of individuals normal weight (N) or overweight or obese (O) and metabolically healthy at baseline remaining metabolically healthy at successive visits. Number, n , are numbers at first visit who were MH

Visits	1+ visits		2+ visits		3+ visits		4+ visits		5+ visits		6+ visits		7+ visits		8+ visits		9+ visits		10+ visits		n-weighted average
	N	O	N	O	N	O	N	O	N	O	N	O	N	O	N	O	N	O	N	O	
n	425	90	225	41	153	30	108	25	77	17	59	16	46	15	32	11	22	7	9	4	N O
Percentage remaining metabolically healthy																					
1	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2			71 [§]	49 [§]	68 [§]	57 [§]	67 [§]	60 [§]	68 [§]	59 [†]	70 [§]	57 [†]	66 [§]	54 [†]	60 [§]	55 [*]	55 [§]	43 [*]	67	25 [*]	68
3					53 [*]	44	50 [*]	44	50 [*]	48	55	44	53	47	44	46	41	29	45	25	51
4							40	36	38	36	45	32	42	34	41	46	41	29	45	25	41
5									28	30	31	25	29	27	32	37	41	15	45	0	31
6											29	25	29	27	32	37	41	15	45	0	32
7													22	27	22	37	28	15	34	0	24
8															16	28	19	15	23	0	18
9																	10	0	12	0	11
10																			12	0	12

Proportions compared with preceding visit – significances: [§] $P<0.001$; [†] $P<0.01$; ^{*} $P<0.05$.

Figure 1

Proportions of individuals overweight or obese (OWOB–dashed line) or normal weight (NW–solid line) and metabolically healthy at baseline remaining metabolically healthy. Attrition of metabolic health is illustrated by plotted series of observations for sub-groups that had 6 or more, 7 or more or 8 or more visits.

Changes in MH status during follow-up

A constant prevalence from one visit to the next might be sustained by equal numbers transitioning from MH to MUH and from MUH to MH. Therefore, we analysed proportions of individuals MH at baseline who remained MH at successive visits. Proportions of individuals MH and OWOB at baseline who remained MH at visit 2

varied between 49 and 60% for number-of-visits sub-groups 1–8 (sub-groups 9 and 10 having unreliably small numbers of observations: $n < 10$), with little evidence of any trend (Table 3). For NW individuals, the range for number-of-visits sub-groups 1–10 was between 60 and 71%. Weighted average proportions of individuals OWOB and MH at baseline who remained MH at visits 2, 3 and 4 were 54, 48 and 39% respectively. From visit 5 onwards, proportions remaining MH continued to decline, but, overall, only the difference in proportions between visits 1 and 2 was statistically significant. Proportions of individuals NW and MH at baseline who remained MH at visits 2, 3 and 4 were 68, 51 and 41%, with the difference in proportions between visits 1 and 2 being generally significant at $P < 0.001$ and between visits 2 and 3, at $P < 0.05$. Initially, the rate of attrition of individuals remaining MH was faster among individuals OWOB at baseline than among those NW (Fig. 1), and for those with ≥ 2 visits, the proportion of OWOB individuals remaining MH at visit 2 was significantly lower than the proportion of NW individuals remaining MH ($P = 0.007$). However, beyond visit 2, proportions of OWOB and NW participants remaining MH converged. For those with ≥ 3 visits, analysis of individuals remaining MH was repeated with visit 2 as baseline, and for those with ≥ 4 visits, visit 3 as baseline. Findings were generally consistent with the analysis with an individual's visit 1 as baseline (Table 4).

Changes in weight and lifestyle during follow-up

For those with ≥ 2 visits, 29% of those OWOB at visit 1 were NW at visit 2. For those with ≥ 3 visits, 15% of those

Table 4 Weighted average percentages of individuals metabolically healthy at baseline remaining metabolically healthy. Data for up to 3 visits subsequent to the baseline visit are shown, with baseline visits taken as an individual's first, second or third visit. Weighted average percentages derive from subsets of individuals with 2, 3, 4 to 10 or more visits.

Baseline visit	% remaining metabolically healthy		
	2nd visit	3rd visit	4th visit
Normal weight			
Visit 1	68	51	41
Visit 2	68	47	38
Visit 3	66	54	49
Overweight or obese			
Visit 1	54	48	39
Visit 2	70	55	39
Visit 3	56	39	41

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OWOB at visit 2 were NW at visit 3. For those with ≥ 4 visits, 23% of those OWOB at visit 3 were NW at visit 4. Equivalent figures for NW individuals becoming OWOB were 6, 8 and 7%. For visits 5–10, proportions ranged between 6 and 16% for OWOB switching to NW and 0 and 9% for NW to OWOB. Transition from OWOB to NW tended to be associated with transition from MUH to MH, although the majority did not change status (results not shown). For the transition from NW to OWOB, again, the majority did not change status. Transitions in smoking, alcohol consumption and exercise were also explored (results not shown). There was a tendency towards reduction in smoking over successive visits but with no clear association with change in MH status. On Cox proportional hazards modelling of incident MUH in the dataset including follow-up visits, only increasing age was a consistent predictor of transition to MUH in those MH at baseline (Model 1: HR: 1.06, 95% CI: 1.03–1.08, $P < 0.001$; Model 2: HR: 1.05, 95% CI: 1.03–1.07, $P < 0.001$; Model 3: HR 1.03, 95% CI: 1.01–1.04, $P < 0.001$). There was some evidence for moderate exercise reducing risk of transition to MUH (Model 1: HR: 0.70, 95% CI: 0.47–1.02, $P = 0.06$; Model 2: HR: 0.73, 95% CI: 0.57–0.93, $P = 0.01$) and for heavy smoking increasing risk (Model 3: HR: 1.47, 95% CI: 0.99–2.16, $P = 0.05$), but, importantly, there was no evidence from any of these analyses that among those MH at baseline those who were OWOB were at an overall increased risk of becoming MUH subsequently.

Discussion

We evaluated three hypotheses. The first was that MH OWOB individuals are at greater risk of CVD mortality than MH NW individuals. This was not the case. Other studies (11, 26) have noted that MH OWOB individuals tend to appear somewhat healthier in terms of weight and lifestyle characteristics than their MUH counterparts, although in our study, this was only apparent with regard to exercise; smoking and alcohol intake tended to be greater in the MH OWOB participants. Overall, however, risk differentials were independent of lifestyle covariates, which accords with the possibility that among OWOB individuals, a low CVD risk sub-group can indeed be distinguished using MH criteria and supports the concept of metabolically healthy overweight or obesity and this low risk may extend to total mortality.

The second hypothesis was that MH OWOB individuals are insulin resistant and exhibit sub-clinical inflammation relative to MH NW individuals. This was the case and, with

regard to inflammation, accords with a previous report of increased inflammation in MHO individuals (27). This could suggest that further discrimination of MH among OWOB individuals may be possible using measures of insulin resistance and sub-clinical inflammation. However, our finding that MH OWOB individuals were at no greater risk of CVD mortality than MH NW individuals suggests that such further discrimination may add little to CVD risk evaluation, consistent with CVD risk associated with increasing adiposity being fully explained by established risk factors (28). However, although increased sub-clinical inflammation in MHO may be relatively benign with regard to CVD risk, the increased insulin resistance may indicate increased risk of type 2 diabetes (26, 29, 30).

Our third hypothesis was that MH in OWOB individuals is a persistent trait, sustained over long-term follow-up. Against this, from visit 1 to 2, fully 51% of MH individuals who were OWOB and 29% of those who were NW and at visit 1 were MUH at visit 2. Subsequently, over two decades of follow-up and with up to 10 visits, only about 30% of individuals either OWOB or NW and MH at baseline remained consistently MH. Moreover, similar percentages transitioned from MUH to MH over the course of these visits (results not shown). That MH is susceptible to this degree of variability does not appear to have been realised in previous studies of MHO or MH OWOB.

Our long-term MH profiles therefore indicate appreciable intra-individual variation in MH status, and this would be expected from the individual variation exhibited by the variables used to categorise MH status (31). Use of a categorical criterion, deriving from a continuous measure of a biologically variable parameter, measured on a single occasion to classify individuals as having or not having a condition is highly susceptible to regression towards the mean, and judging by the marked attrition in MH individuals from visit 1 to 2, this had considerable impact on MH categorisation. Beyond visit 2, however, the rate of attrition of individuals consistently MH was reduced somewhat. Importantly, however, in survival analysis with incident MUH as outcome, among those who were MH at baseline, OWOB was entirely unrelated to transition to MUH; moreover, transition to MUH could not be accounted for by weight gain and was only associated with lifestyle change to a limited extent, consistent with MH at baseline being, to some extent, a stable characteristic. We may, therefore, infer that each participant in the study had an underlying degree of metabolic health that was further from or closer to the categorical cut-offs applied to define MH. Those far from the cut-offs would have tended to retain MH or MUH

status, whereas those close to the cut-off would have transitioned from one state to another over time. It is noteworthy, however, that the proportion of individuals transitioning from MH to MUH from visit 1 to 2 was significantly greater among OWOB than among NW individuals. Possibly, given that MH was less prevalent among OWOB individuals, classifications of MH at baseline might be more susceptible to greater extremes of variation, which would be more likely to relapse into MUH at a second visit.

A number of previous studies have evaluated CVD risk in MH OB. In accord with our findings, despite inconsistencies in the definitions of MH, the majority have found CVD risk to not be increased in MH OB compared with MH NW individuals (18, 26, 29, 32, 33, 34, 35), or have found CVD risk to be lower in MH OB compared with MUH OB (36), but not all studies agree (10). Moreover, several studies have found evidence for increased risk in MH OB compared with MH NW individuals in studies with >15 years follow-up (17, 19, 37). However, our findings, which concerned CVD mortality over >20 years of follow-up, did not bear this out.

Few previous studies have included a follow-up evaluation of MH status. Appleton *et al.* undertook baseline and follow-up evaluation in a population sample of 3743 individuals over a median of 8.2 years with 61% providing clinic data at follow-up (26). In agreement with our findings, a significantly higher proportion of MH OB than MH NW individuals were MUH at a second visit and risk of CVD in the MH OB was no greater than in MH NW individuals. Also, in accord with our findings, the proportion of individuals MHO at baseline becoming MUH at follow-up was substantial at 30%. Likewise, Soriguer *et al.*, in a study of 1051 individuals, found that 48% of those MH OB at baseline were MUH at a 6-year follow-up (30). However, in neither of these studies was the time profile of attrition of MH distinguished, there being only a single follow-up estimate of change in MH status.

A limitation of our study was the relatively small sample size, potentially exacerbated by exclusion of 92 participants due to missing data. Analysis of the dataset with imputation of missing values resulted in identical findings with regard to CVD mortality (results not shown). However, with the imputed dataset, having 1 risk factor was associated with increased risk of total mortality. Further sub-analysis with MH defined by having no risk factors confirmed relative protection for total mortality among MH OWOB individuals, but there were no CVD deaths among OWOB participants with no risk factors. It should be acknowledged that the

non-significant hazard ratio of 1.66 we observed for CVD mortality among those with a single risk factor could become statistically significant with greater numbers, so our definition of metabolic health must be regarded as relative and no more than a working definition. It should also be acknowledged that allowing for a single risk factor in our definition of MH could lead to inclusion of people with diabetes as metabolically healthy. This might seem unjustified; however, it should be borne in mind that a participant with diabetes as a sole risk factor would have to have been free of abnormalities in all other risk factors and not be taking lipid- or blood pressure-lowering agents. In any case, exclusion of people with diabetes from our analysis made no difference to our findings (results not shown). The small numbers of clinical outcomes meant that we could not systematically analyse CVD risk according to change in MH status, as has been done in one previous study, which was able to demonstrate that risk of CVD in the MHO was no greater than in MH NW individuals regardless of subsequent transition to MUH (26). Nevertheless, in accord with this, we could conclude that despite appreciable transitioning between MH and MUH, OBOW individuals who were MH at baseline were not at increased risk. Limitations also included the highly selected group, which limits generalisability, although its homogeneity represents a strength with respect to hypothesis testing. Another limitation was the progressive loss to follow-up with regard to metabolic testing. It should be noted that our follow-up was undertaken in the context of a health program and there was evidence for weight loss in the cohort overall. Weight loss might have been expected to reduce transitioning from MH to MUH and possibly contributed to an increase in the prevalence of MH among individuals OBOW at baseline up to visit 3.

In conclusion, our findings indicate appreciable individual variability and regression towards the mean when MH status is assigned by widely used criteria. MH among OW and OB individuals was associated with increased insulin resistance and sub-clinical inflammation compared with MH NW individuals. Nevertheless, despite these differences, OWOB individuals classified as MH at baseline according to either definition of MH were at no greater risk of CVD mortality over two decades of follow-up than MH NW individuals, supporting the possibility that a discrete category of metabolically healthy overweight or obesity can be distinguished.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0095>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

A K: statistical analysis, manuscript writing; D G J: analysis plan and manuscript development, IFG analysis plan, statistical analysis, manuscript writing.

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