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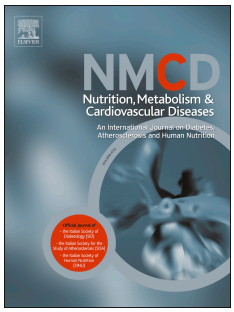

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Contribution of 20-year body mass index and waist circumference history to poor cardiometabolic health in overweight/obese and normal weight adults: a cohort study

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Abbreviations
BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; MHNW, metabolically healthy normal weight; MHOO, metabolically healthy overweight/obese; MUNW, metabolically unhealthy normal weight; MUOO, metabolically unhealthy overweight/obese; SBP, systolic blood pressure; WC, waist circumference

Key words
Obesity, cardiometabolic health, histories, severity, duration, variability, Whitehall II study

Abstract

Background and Aims: We investigated the associations of 20-year body mass index (BMI) and waist circumference (WC) histories with risk of being 1) metabolically unhealthy overweight/obese (MUOO) vs metabolically healthy overweight/obese (MHOO) and 2) metabolically unhealthy normal weight (MUNW) vs metabolically healthy normal weight (MHNW).

Methods and Results: Participants comprised 3,018 adults (2,280 males; 738 females) with BMI and WC measured, every ~5 years, in 1991-1994, 1997-1999, 2002-2004, 2007-2009, and 2012-2013. Mean age in 2012-2013 was 69.3 years, with a range of 59.7-82.2 years. Duration was defined as the number of times a person was overweight/obese (or centrally obese) across the 5 visits, severity as each person's mean BMI (or WC), and variability as the within-person standard deviation of BMI (or WC). At the 2013-2013 visit, participants were categorised based on their weight (overweight/obese or normal weight; body mass index (BMI) ≥25 kg/m^2) and health status (healthy or unhealthy; two or more of hypertension, low high-density lipoprotein cholesterol, high triglycerides, high glucose, and high homeostatic model assessment of insulin resistance). Logistic regression was used to estimate associations with the risk of being MUNW (reference MHNW) and MUOO (reference MHOO) at the last visit. BMI and WC severity were each related to increased risk of being unhealthy, with estimates being stronger among normal weight than overweight/obese adults. The estimates for variability exposures became null upon adjustment for severity. Individuals who were overweight/obese at all 5 time points had a 1.60 (0.96-2.67) times higher risk of being MUOO than MHOO compared to those who were only overweight/obese at one (i.e., the last) time point. The corresponding estimate for central obesity was 4.20 (2.88-6.12). Greater duration was also related to higher risk of MUNW than MHNW.

Conclusion: Being overweight/obese yet healthy seems to be partially attributable to lower exposure to adiposity across 20 years of adulthood. The results highlight the importance of maintaining optimum and stable BMI and WC, both in adults who become and do not become overweight/obese.

Introduction

Obesity is a major public health concern because it increases risk for many cardiometabolic complications such as type 2 diabetes.[1 2] Cardiometabolic health profiles are, however, not the same for all obese individuals, which has given rise to the controversial concept of "metabolically healthy obesity" (MHO).[1 3 4] The literature on MHO and metabolically healthy overweight/obesity (MHOO) has largely focused on rebutting the idea that someone can be healthy yet overweight or obese by demonstrating how such individuals transition to being unhealthy more frequently,[5-8] and have increased disease risk,[9 10] compared to metabolically healthy normal weight (MHNW) individuals.

While much work has prospectively examined baseline MHO or MHOO and incident disease, very few studies have looked back in time and modelled the life course processes and exposures that explain why some overweight or obese adults develop poor cardiometabolic health while others do not.[11-13] Similarly, few studies have investigated the life course epidemiology of poor metabolic health among non-obese individuals.[14] It may be hypothesised that metabolically unhealthy overweight/obese (MUOO) and metabolically unhealthy normal weight (MUNW) individuals have experienced greater exposure to the adverse effects of BMI across life. Supporting this, studies have found a higher mean BMI in the MUOO group compared to the MHOO group (and in the MUNW group compared to the MHNW group).[15] Because central obesity has effects on cardiometabolic health and mortality risk independent of general obesity,[16] it is also probable that waist circumference (WC) history is related to the risk of being unhealthy.[17] This might be particularly true in the normal weight group, given the strong evidence on the association between normal weight central obesity and mortality.[18]

Two key existing papers have examined links between duration of obesity and metabolic status.[19 20] The Mongraw-Chaffin et al study investigated the association of obesity duration and severity, over 10 years, with metabolic syndrome in 2,748 adults in the Multi-Ethnic Study of Atherosclerosis. This paper did not, however, consider MUNW or waist circumference traits, and the main analysis was not clearly restricted to metabolic syndrome development among obese individuals. Using data on 1,040 participants in the EPITeen cohort, the Craveiro et al study investigated the associations of area under the BMI curve between 13-24 years of age with a binary metabolic health outcome at 24 years among individuals who were overweight or obese at 24 years and, separately, among individuals who were underweight or normal weight at 24 years. A one-unit higher BMI per year was associated with 0.92 (0.85, 1.00) times lower odds of being metabolically healthy in the overweight/obese group and 0.86 (0.78, 0.94) times lower odds in the under/normal weight group. Comparable estimates based on adulthood exposure to BMI (and WC) are not available in the literature, despite clearly being important for preventive medicine knowledge and public health messaging.

The present paper aimed to investigate the association of BMI and WC history with risk of being MUOO vs MHOO and MUNW vs MHNW. We characterised the exposure history in terms of severity and variability of BMI and WC over 20-years, and duration of overweight/obesity and central obesity. We also examined the extent to which differences in cardiometabolic risk factors (e.g., systolic blood pressure (SBP)) between unhealthy and healthy groups might be explained by BMI and WC history.

Methods

Study sample

The Whitehall II study was established to explore the relationship between socio-economic position, stress, and cardiovascular disease.[21] A cohort of 10,308 (6,895 men; 3,413 women) civil servants aged 35-55 years, working in London, United Kingdom (UK) for the

government, participated in an examination in 1985-1988. A combination of clinical and questionnaire data from five repeated assessments (1991-1994, 1997-1999, 2002-2004, 2007-2009, and 2012-2013) over approximately two decades of follow-up were used in the present paper. The mean (SD) times in between consecutive visits were 5.8 (0.4), 5.4 (0.4), 5.0 (0.1) and 4.1 (0.2) years in our sample. The University College London research ethics committee granted ethical approval for each phase of data collection. Participants provided written informed consent.

Starting with the 6,318 cohort members who were still participating in the study in 2012-2013, 1,697 were excluded because of missing clinical data necessary to define weight/health status in 2012-2013; 62 because their BMI in 2012-2013 was classified as thin (i.e., < 18.5 kg/m^2); 488 because of missing covariate data in 1994-1994; and 1,053 because of missing BMI data in 1991-1994, 1997-1999, 2002-2004, and/or 2007-2009. The resulting sample comprised 3,018 individuals. Out of these individuals, 367 did not have complete data on WC across the five sweeps. A slightly smaller sample of 2,651 (i.e., 3,018-367) is therefore used for WC analyses.

Exposures

At each assessment, weight, height, and WC (at the widest point) were measured by a trained nurse according to standardized protocols. All measurements were taken in duplicate, with a third recording taken if the first and second differed by more than pre-defined limits. We used an average of the first two recordings or an average of the two nearest values (if three recordings were taken). BMI was calculated as weight (kg) / height (m)^2. Overweight/obesity was defined as a BMI ≥25 kg/m^2 and central obesity was defined as a WC ≥102 cm in males or ≥88 cm in females.[22] We constructed three measures of BMI and WC history: Duration was defined as the number of times a person was overweight/obese (or centrally obese) across the five sweeps, ranging from 0 to 5. Severity was defined as each person's mean BMI (or WC) across the five sweeps. Variability was defined as the within-person standard deviation of BMI (or WC) across the five sweeps.

Outcomes

In 2012-2013, SBP and diastolic blood pressure (DBP) were assessed by a trained nurse according to standardized protocols and fasting blood samples were taken for biochemical analysis of high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, and insulin levels, as previously described.[5 6 15 23] Use of hypertension medication (diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and other anti-hypertensives), diabetes medication (insulin and oral antidiabetic drugs), and cardiovascular disease medication (antihypertensives, nitrates, antiplatelets, and lipid-lowering drugs) medication were reported (yes vs no). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting glucose (mmol/L) X fasting insulin (mmol/L) / 22.5. On the basis of independent criteria,[24] and as in previous Whitehall II publications,[5 6 15 23] health status was defined as healthy if participants had zero or one of the following five cardio-metabolic disease risk factors and unhealthy if they had two or more: blood pressure ≥130/85 mmHg or use of hypertension medication, HDL-C <1.03 mmol/L for men and <1.29 mmol/L for women, triglycerides ≥1.7 mmol/L, fasting plasma glucose ≥5.6 mmol/L or use of diabetes medication, and HOMA-IR >5.1 (90th percentile in the sample). Individuals were then categorised as being MHNW, MUNW, MHOO, or MUOO.

Covariates

Covariates at baseline in 1991-1994 were assessed via a questionnaire and coded as follows. Sex (female vs male) and ethnicity (non-white vs white) were recorded in addition to socio-economic position based on occupational role (clerical/support, administrative, vs professional/executive). The following health behaviours were also assessed: frequency of alcohol consumption (daily, weekly or monthly, vs never or special occasions), smoking status (current, ex, vs never), and frequency of mild and moderate exercise (1-3

times/month or seldom, 1-2 times/week, vs 3 times/week or more). The General Health Questionnaire (GHQ-30) was administered to capture psychological distress and was coded as high distress (10-30), moderate (2-9), vs none (0-1).[25] We also used age in decimal years from the 2012-2013 sweep.

Statistical analysis

Descriptive statistics for each variable used in the analysis were produced, stratified by weight/health status (i.e., MHNW, MUNW, MHOO, or MUOO).

Multinomial logistic regression was used to estimate the associations of the BMI and WC severity and variability exposures with the weight/health status outcome. Each exposure was tested separately, before fitting models that were mutually adjusted for BMI (or WC) severity and variability. All models were adjusted for sex, ethnicity, age at outcome, and alcohol intake, mild and moderate exercise, educational attainment, and GHQ score. Estimates are presented for the risk of being MUNW vs MHNW and for the risk of being MUOO vs MHOO.

Binary logistic regression was used to estimate the associations of overweight/obesity and central obesity duration with the risk of MUOO vs MHOO. This analysis was also performed for a MUNW vs MHNW outcome but using a reduced number of duration categories (0, 1, ≥2) because most MUNW and MHNW participants were never overweight/obese or centrally obese. Again, all models were adjusted for sex, ethnicity, age at outcome, and alcohol intake, mild and moderate exercise, educational attainment, and GHQ score.

General linear regression was used to estimate the covariate-adjusted differences in SBP, DBP, triglycerides, HDL-C, glucose, and HOMA-IR between MUOO vs MHOO individuals and, separately, between MUNW vs MHNW individuals. These models were then re-run to ascertain the extent to which the estimates attenuated upon adjustment for BMI (or WC) severity and variability. Because some variables were skewed, and to aid comparison of effect sizes, the transformation $y = 100\ln(x)$ was used for all outcomes. Estimates are symmetric percentage differences.[26]

Sensitivity analysis

All analyses were re-run using weight/health status groups defined according to BMI ≥30 kg/m^2. In these analyses, we considered duration of obesity rather than duration of overweight/obesity.

All procedures were performed in Stata 15 (StataCorp LP, College Station, TX, USA).

Results

Table 1 shows descriptive statistics of the study sample, according to weight/health status. The mean age of the sample in 2012-2013 was 69.3 years, with a range of 59.7-82.2 years. Approximately 61% of the sample was overweight/obese and 37% of these individuals were unhealthy. Despite both the MHOO and MUOO groups being labelled as overweight/obese in 2012-2013, severity and variability of BMI and WC across the preceding 20 years were higher in the MUOO group. 69% of individuals in the MUOO group had been overweight/obese at all prior time points, compared to 56% in the MHOO group. Among the 39% of the sample that was normal weight only 14% were unhealthy. Severity, but not variability, of BMI and WC were higher in the MUNW than MHNW group. 61% of individuals in the MUNW group were not overweight/obese at any of the five time points, compared to 74% in the MHNW group.

The severity exposures were related to increased risk of being unhealthy, with estimates tending to be stronger among normal weight adults than overweight/obese adults (Table 2). For example, a one kg/m^2 increase in BMI severity was related to a 1.23 (1.10, 1.38) times

increased risk of being MUNW compared to MHNW and a 1.15 (1.11, 1.18) times increased risk of being MUOO compared to MHOO. The variability exposures were also associated with increased risk of being unhealthy, with the exception that WC variability was only associated with a 1.05 (0.96, 1.15) times increased risk of being MUNW vs MHNW. In models that were mutually adjusted for BMI (or WC) severity and variability, the estimates for variability attenuated and became null.

Individuals who were overweight/obese at all 5 time points had a 1.60 (0.96, 2.67) times higher risk of being MUOO than MHOO compared to those who were only overweight/obese at one (i.e., the last) time point (Table 3). Interestingly, however, overweight/obesity durations of 3 or 4 were not related to increased risk of MUOO at alpha 5%, and an overweight/obesity duration of 2 was associated with a 0.46 (0.23, 0.96) times lower risk of MUOO. Estimates for duration of central obesity were stronger and all in the expected direction. Greater duration was also related to higher risk of MUNW than MHNW, again with effect sizes being strongest for central obesity. Individuals who were centrally obese at ≥2 time points had a 3.06 (1.23, 7.60) times higher risk of being MUNW than MHNW compared to those who were not centrally obese at any time point.

Table 4 presents the estimated differences between MUOO and MHOO adults in continuous cardiometabolic disease risk factors. All of the estimates were attenuated after adjustment for BMI (or WC) severity and variability. For example, the MUOO group were estimated to have a 2.1% (1.0, 3.3) higher SBP than the MHOO group, but this estimate attenuated to 1.8% (0.7, 3.0) after adjustment for BMI severity and variability. This suggests that approximately 14% of the higher SBP in the MUOO group is explained by their more deleterious BMI severity and variability over the preceding 20 years. The degree of attenuation was highest for DBP, although both the unadjusted and adjusted estimates were not precise, with p-values > 0.2. Regardless of whether we adjusted for BMI or WC traits, the strongest evidence of attenuation was observed for SBP, HDL-C, and HOMA-IR. A similar pattern of results was found in the MUNW vs MHNW comparison (Table 5).

Results of the sensitivity analysis, using weight/health status groups defined according to BMI ≥30 kg/m^2, are shown in Supplementary Tables 1-4. Results were similar to the main analysis, with the exception that duration of obesity (and duration of central obesity) was not related to risk of poor metabolic health in obese adults, likely due to the small numbers (e.g., only 26 individuals in the MHO group had an obesity duration of 1).

Discussion

The key finding of the present paper is that BMI and WC severity over 20 years are related to increased risk of poor cardiometabolic health in normal weight and overweight/obese adults, even after adjusting for variability (of BMI and WC). A history of persistent central obesity was found to be the strongest risk factor for poor cardiometabolic health. Our results also, however, suggest that greater exposure to excess adiposity only partly explain the elevated disease risk factors of unhealthy (compared to healthy) normal weight adults and overweight/obese adults.

There is a reasonably large literature base on obesity severity and duration in relation to cardiometabolic health.[20 27-30] A recent paper by Norris et al, for example, investigated duration of obesity (and total exposure to BMI, above the obesity threshold) between 10-40 years in 20,746 participants in three British birth cohort studies.[27] Greater duration was related to higher subsequent SBP, HDL-C, and HbA1c, with the estimate for HbA1c remaining significant even after adjusting for severity. The present paper provides information beyond that type of study (e.g., Norris et al) by considering how associations might differ between normal weight and overweight/obese adults.

The concept of MHO has been widely debated, largely because such individuals have increased risk of various non-communicable diseases (e.g., type 2 diabetes and chronic kidney disease) and higher mortality compared to their MHNW counterparts.[3 9 10] Far fewer studies have, however, investigated the life course processes and factors that result in some obese people having poor cardiometabolic health while other obese people do not.[11-13]. Our results are in broad agreement with the study of Craveiro et al, which reported that a one-unit higher BMI per year (on average) between 13-24 years was associated with a 0.92 (0.85, 1.00) times lower odds of being metabolically healthy among individuals who were overweight/obese at 24 years.[19] In the normal weight adults, the equivalent estimate was 0.86 (0.78, 0.94), therefore suggesting that exposure to BMI is more strongly related to cardiometabolic health in normal weight than overweight/obese adults. In our larger, longer-term study of adults, we similarly found stronger estimates, of the association between BMI severity over 20 years and cardiometabolic health, in normal weight adults.

The present study also found that greater variability in BMI across 20 years was related to increased risk of poor cardiometabolic health. This finding is consistent with studies showing that weight variability and fluctuations are related to increased risk of type 2 diabetes, cardiovascular disease, and mortality.[31-33] For example, using data on 4,796 Japanese atomic bomb survivors, with biennial measurements over a 20 year baseline period, Cologne et al reported that within-individual variability in BMI was positively related to risk of all-cause and ischemic heart disease mortality over a subsequent 27 year period.[32] Our results provide new evidence that such associations might be present in both normal weight and overweight/obese adults. While the estimates of Cologne et al were independent of individual predictions (from a multilevel growth model) of BMI at 44 years and the linear rate of change in BMI, our estimates became null after adjusting for BMI severity. These are, however, different approaches and the observed attenuation in our analysis make sense given the known correlation between BMI variability and severity (ρ = 0.52 in our sample).[27]

Similar to the study of Mongraw-Chaffin et al,[20] which investigated the association of obesity severity and duration over 10 years with incident metabolic syndrome in the Multi-Ethnic Study of Atherosclerosis, we found that Whitehall II participants who were always overweight/obese had a 1.60 (0.96, 2.67) times higher risk of being MUOO than MHOO. The estimates for central obesity were, however, stronger and demonstrated a clearer dose-response relationship. This is consistent with the notion that central obesity is more harmful than general overweight/obesity.[34 35] Duration of central obesity was also positively related to risk of MUNW compared to MHNW, which might be expected given knowledge that central obesity has effects on cardiometabolic health and mortality risk independent of general overweight/obesity.[16 18]

The small literature base on MHO and duration/severity of obesity has focused on reporting associations.[19 20 36] No previous studies have, however, documented the extent to which differences in continuous risk factors between unhealthy and healthy groups (e.g., MUOO vs MHOO) might be explained by life course BMI (and WC) traits. Our analysis shows that severity and variability of WC over 20 years accounted for approximately 10% of the higher SBP, HDL-C, and HOMA-IR of the MUOO compared to the MHOO group. These, and all other, estimates were smaller than expected, perhaps because the participants in our sample were already 40-63 years old in 1994-1994 (i.e., at the first measurement). Recently published data shows that childhood obesity affects risk of coronary artery disease and type 2 diabetes largely via adulthood obesity,[37] but that does not mean that our results would not change if we were able to investigate BMI (and WC) traits over, for example, 40 years instead of 20 years. BMI is not a measure of adiposity,[38] and adjustment for more specific measures, like visceral adipose tissue severity and variability,[39] may have also resulted in greater attenuation of the estimated differences in risk factors between unhealthy and healthy groups. Nonetheless, our results demonstrate that while life course obesity severity

and duration measures might be related to risk of MUOO vs MHOO (and MUNW vs MHNW), they might not sustainably explain the worse risk factor profile of the unhealthy group.

The main strength of the present article is the thorough analysis of longitudinal data collected over 20 years of follow-up to address a novel research question. In terms of limitations, the Whitehall II study sample is not representative of the wider UK population, although standard risk factor-cardiovascular disease associations in Whitehall II are comparable to those found in nationally representative studies.[40] Approximately 30% of the initial cohort participated in the 2012-2013 sweep and had the necessary data for analysis, thus differential selection into our sample may have biased results.[41] Owing to our sample size and small numbers in some groups (e.g., MHOO individuals with duration of obesity of 1) we did not think it was prudent to test for effect modification by sex and baseline age.

Conclusion

This paper further challenges the concept of MHO by showing that this condition represents, at least partially, a lower level of exposure to excess adiposity across 20 years of adulthood. The results also demonstrate the importance of maintaining optimum and stable BMI and WC, even in adults who do not become obese. Further research with life course data is needed to fully explain the worse cardiometabolic health profile of MUOO compared to MHOO (and MUNW compared to MHNW) adults.

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Author contributions
ER and WJ conceptualized the study. ER carried out the analyses and drafted the initial manuscript. TN, SC, MK, MH, and WJ made substantial contributions to the interpretation of the data, revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Competing interest's statement
The authors declare that they have no conflict of interest.

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Table 1. Description of study sample, according to weight/health status in 2012/13

			MHNW N=1,020 (33.8%)	MUNW N=163 (5.4%)	MHOO N=1,162 (38.5%)	MUOO N=673 (22.3%)
Baseline demographics (1991/94)	Sex					
	Male	N (%)	737 (72.3)	138 (84.7)	879 (75.7)	526 (78.2)
	Female	N (%)	283 (27.8)	25 (15.3)	283 (24.4)	147 (21.8)
	Ethnicity					
	White	N (%)	966 (94.7)	133 (81.6)	1,102 (94.8)	612 (90.9)
	Non-white	N (%)	54 (5.3)	30 (18.4)	60 (5.2)	61 (9.1)
	Smoking					
	Never	N (%)	592 (58.0)	77 (47.2)	586 (50.4)	304 (45.2)
	Ex	N (%)	361 (35.4)	67 (41.1)	466 (40.1)	272 (40.4)
	Current	N (%)	67 (6.6)	19 (11.7)	110 (9.5)	97 (14.4)
	Alcohol intake					
	Never or special occasions	N (%)	112 (11.0)	29 (17.8)	135 (11.6)	93 (13.8)
	Weekly or monthly	N (%)	534 (52.4)	82 (50.3)	608 (52.3)	344 (51.1)
	Daly	N (%)	374 (36.7)	52 (31.9)	419 (36.1)	236 (35.7)
	Mild exercise					
	Three times/week or more	N (%)	721 (70.7)	113 (69.3)	804 (69.2)	437 (64.9)
	1-2 times/week	N (%)	262 (25.7)	38 (23.3)	290 (25.0)	185 (27.5)
	1-3 times/month or seldom	N (%)	37 (3.6)	12 (7.4)	68 (5.9)	51 (7.6)
	Moderate exercise					
	Three times/ week or more	N (%)	188 (18.4)	32 (19.6)	182 (15.7)	94 (14.0)
	1-2 times/week	N (%)	483 (47.4)	71 (43.6)	567 (48.8)	297 (44.1)
	1-3 times/month or seldom	N (%)	349 (34.2)	60 (36.8)	413 (35.5)	282 (41.9)
	Grade					
	Professional or executive	N (%)	442 (43.3)	83 (50.9)	529 (45.5)	321 (47.7)
	Administrative	N (%)	514 (50.4)	61 (37.4)	520 (44.8)	278 (41.3)
	Clerical or support	N (%)	64 (6.3)	19 (11.7)	113 (9.7)	74 (11)
	GHQ					
	0-1	N (%)	536 (52.6)	102 (62.6)	587 (50.5)	360 (53.5)
	2-9	N (%)	347 (34.0)	47 (28.8)	425 (36.6)	231 (34.3)
	10-30	N (%)	137 (13.4)	14 (8.6)	150 (12.9)	82 (12.2)
Exposure variables (1991/94 to 2012/13)	BMI severity	Mean (SD)	22.9 (1.7)	23.5 (1.4)	27.6 (2.9)	28.8 (3.5)
	BMI variability	Mean (SD)	0.9 (0.5)	0.9 (0.5)	1.4 (0.8)	1.5 (0.9)
	Duration of overweight/obesity					
	0	N (%)	756 (74.1)	100 (61.4)	0	0

	1	N (%)	99 (9.7)	23 (14.1)	53 (4.6)	23 (3.4)
	2	N (%)	84 (8.2)	17 (10.4)	84 (7.2)	17 (2.5)
	3	N (%)	40 (3.9)	16 (9.8)	125 (10.8)	62 (9.2)
	4	N (%)	41 (4.0)	7 (4.3)	247 (21.3)	109 (16.2)
	5	N (%)	0	0	653 (56.2)	462 (68.7)
	WC[a] severity	Mean (SD)	83.3 (7.2)	87.4 (6.5)	95.5 (8.3)	99.8 (9.3)
	WC variability	Mean (SD)	4.6 (2.1)	4.4 (2.0)	6.2 (2.8)	6.5 (3.0)
	Duration of central obesity					
	0	N (%)	809 (90.0)	120 (82.8)	372 (36.7)	143 (23.7)
	1	N (%)	62 (6.9)	17 (11.7)	170 (16.8)	84 (13.9)
	2	N (%)	14 (1.6)	6 (4.1)	144 (14.2)	68 (11.3)
	3	N (%)	7 (0.8)	2 (1.4)	122 (12.0)	86 (14.3)
	4	N (%)	6 (0.7)	0	125 (12.3)	116 (19.2)
	5	N (%)	1 (0.1)	0	81 (8.0)	106 (17.6)
Cardiometabolic variables (2012/13)	Age	Mean (SD)	69 (5.7)	71 (5.8)	69.1 (5.6)	69.6 (5.6)
	SBP (mmHg)	Mean (SD)	124.1 (16.2)	128.9 (18.5)	126.5 (14.7)	129.4 (16.5)
	DBP (mmHg)	Mean (SD)	68.6 (9.6)	68.9 (11.5)	71.2 (9.0)	71.3 (10.1)
	Triglycerides (mmol/L)	Median (IQR)	0.8 (0.4)	1.2 (0.9)	1.0 (0.5)	1.5 (0.9)
	HDL-C (mmol/L)	Mean (SD)	1.8 (0.5)	1.6 (0.5)	1.6 (0.4)	1.4 (0.4)
	Glucose (mmol/L)	Median (IQR)	5.0 (0.5)	5.8 (0.8)	5.1 (0.5)	5.8 (0.9)
	HOMA-IR	Median (IQR)	1.5 (0.9)	2.6 (2.9)	1.9 (1.4)	3.8 (3.6)

Abbreviations. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight or obese; MUOO, metabolically unhealthy overweight or obese.

[a]WC sample (N=2,651): MHNW (N=899, 33.9%), MUNW (N=145, 5.5%), MHOO (N=1,014, 38.2%), MUOO (N=593, 22.4%)

Table 2. Associations of BMI and WC severity and variability (1991/94 to 2012/13) with the risk of being metabolically unhealthy (2012/13)

		MUNW vs MHNW		MUOO vs MHOO	
		RR (95% CI)	p-value	RR (95% CI)	p-value
BMI	Each separately				
	Severity	1.23 (1.10, 1.38)	<0.001	1.15 (1.11, 1.18)	<0.001
	Variability	1.59 (1.10, 2.31)	0.013	1.35 (1.20, 1.53)	<0.001
	Mutually adjusted				
	Severity	1.22 (1.09, 1.37)	0.001	1.13 (1.09, 1.18)	<0.001
	Variability	1.23 (0.85, 1.80)	0.275	1.10 (0.96, 1.27)	0.167
WC					
	Each separately				
	Severity	1.09 (1.05, 1.12)	<0.001	1.06 (1.05, 1.08)	<0.001
	Variability	1.05 (0.96, 1.15)	0.288	1.07 (1.02, 1.11)	0.002
	Mutually adjusted				
	Severity	1.09 (1.05, 1.12)	<0.001	1.06 (1.05, 1.08)	<0.001
	Variability	1.02 (0.93, 1.13)	0.660	1.03 (0.98, 1.07)	0.242

Abbreviations. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight or obese; MUOO, metabolically unhealthy overweight or obese.

All models adjusted for sex, ethnicity, age at outcome, and alcohol intake, mild and moderate exercise, educational attainment, and GHQ score in 1991/94.

Table 3. Associations of overweight/obesity duration and central obesity duration (1991/94 to 2012/13) with the risk of being metabolically unhealthy (2012/13)

		MUNW vs MHNW			MUOO vs MHOO	
		RR (95% CI)	P-value		RR (95% CI)	P-value
Duration of overweight/obesity	0 (referent)			0[a]		
	1	1.63 (0.97, 2.74)	0.067	1[b] (referent)		
	≥2	1.75 (1.15, 2.68)	0.009	2	0.46 (0.23, 0.96)	0.038
				3	1.11 (0.62, 2.00)	0.718
				4	1.02 (0.59, 1.76)	0.941
				5	1.60 (0.96, 2.67)	0.071
Duration of central obesity	0 (referent)			0 (referent)		
	1	2.50 (1.30, 4.81)	0.006	1	1.34 (0.96, 1.87)	0.085
	≥2	3.06 (1.23, 7.60)	0.016	2	1.33 (0.93, 1.90)	0.120
				3	1.95 (1.37, 2.77)	<0.001
				4	2.87 (2.05, 4.02)	<0.001
				5	4.20 (2.88, 6.12)	<0.001

Abbreviations. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight or obese; MUOO, metabolically unhealthy overweight or obese.

All models adjusted for sex, ethnicity, age at outcome, and alcohol intake, mild and moderate exercise, educational attainment, and GHQ score in 1991/94.

[a]A duration of overweight/obesity of 0 in the MUOO and MHOO groups is not possible.
[b]The referent group reflects individuals who were only overweight or obese in 2012/13 when they were categorised as being MUOO or MHOO.

Table 4. Estimated differences in continuous cardiometabolic health measures between MUOO and MHOO adults in 2012/13, before and after adjustment for BMI or WC severity and variability between 1991/94 and 2012/13

		Model 1 Unadjusted for severity and variability		Model 2 Adjusted for severity and variability		Model 2 vs Model 1	
		MUOO vs MHOO		MUOO vs MHOO			
		s% (95% CI)	P-value	s% (95% CI)	P-value	Difference	% difference
BMI	SBP	2.1 (1.0, 3.3)	<0.001	1.8 (0.7, 3.0)	0.002	-0.3	-14.3
	DBP	0.5 (-0.8, 1.8)	0.439	0.1 (-1.1, 1.4)	0.837	-0.4	-80.0
	Triglycerides	37.6 (33.8, 41.4)	<0.001	36.9 (33.0, 40.8)	<0.001	-0.7	-1.9
	HDL-C	-16.8 (-19.0, -14.6)	<0.001	-15.8 (-18.0, -13.6)	<0.001	-1.0	-6.0
	Glucose	16.7 (15.1, 18.2)	<0.001	16.3 (14.8, 17.9)	<0.001	-0.4	-2.4
	HOMA-IR	76.8 (70.7, 82.9)	<0.001	70.1 (64.1, 76.2)	<0.001	-6.7	-8.7
WC	SBP	2.2 (1.0, 3.4)	<0.001	1.9 (0.7, 3.2)	0.002	-0.3	-13.6
	DBP	0.8 (-0.6, 2.1)	0.259	0.4 (-1.0, 1.7)	0.607	-0.4	-50.0
	Triglycerides	36.5 (32.4, 40.6)	<0.001	34.3 (30.1, 38.5)	<0.001	-2.2	-6.0
	HDL-C	-17.5 (-19.9, -15.2)	<0.001	-15.7 (-18.1, -13.3)	<0.001	-1.8	-10.3
	Glucose	16.6 (14.9, 18.2)	<0.001	16.0 (14.3, 17.7)	<0.001	-0.6	-3.6
	HOMA-IR	77.6 (71.1, 84.2)	<0.001	68.9 (62.4, 75.4)	<0.001	-8.8	-11.2

Abbreviations. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight or obese; MUOO, metabolically unhealthy overweight or obese.

s% estimates are symmetric percentage differences.
All models adjusted for sex, ethnicity, age at outcome, and alcohol intake, mild and moderate exercise, educational attainment, and GHQ score in 1991/94.

Table 5. Estimated differences in continuous cardiometabolic health measures between MUNW and MHNW adults in 2012/13, before and after adjustment for BMI or WC severity and variability between 1991/94 and 2012/13

		Model 1 Unadjusted for severity and variability		Model 2 Adjusted for severity and variability		Model 2 vs Model 1	
		MUNW vs MHNW		MUNW vs MHNW			
		s% (95% CI)	P-value	s% (95% CI)	P-value	Difference	% difference
BMI	SBP	2.8 (0.6, 5.0)	0.012	2.7 (0.5, 4.9)	0.018	-0.1	-3.6
	DBP	1.1 (-1.4, 3.6)	0.392	0.9 (-1.6, 3.4)	0.462	-0.2	-18.2
	Triglycerides	32.5 (26.0, 39.1)	<0.001	31.4 (24.8, 38.0)	<0.001	-1.1	-3.4
	HDL-C	-15.4 (-19.4, -11.4)	<0.001	-14.4 (-18.3, -10.4)	<0.001	-1.0	-6.5
	Glucose	18.6 (16.5, 20.8)	<0.001	18.3 (16.1, 20.5)	<0.001	-0.3	-1.6
	HOMA-IR	83.6 (73.4, 93.8)	<0.001	79.6 (69.6, 89.6)	<0.001	-4.0	-4.8
WC	SBP	3.1 (0.8, 5.5)	0.009	3.0 (0.6, 5.4)	0.013	-0.1	-3.2
	DBP	1.9 (-0.7, 4.5)	0.151	1.7 (-1.0, 4.3)	0.212	-0.2	-10.5
	Triglycerides	34.4 (27.5, 41.3)	<0.001	31.4 (24.5, 38.2)	<0.001	-3.0	-8.7
	HDL-C	-16.7 (-20.9, -12.5)	<0.001	-14.9 (-19.0, -10.7)	<0.001	-1.8	-10.8
	Glucose	17.6 (15.4, 19.8)	<0.001	17.3 (15.1, 19.5)	<0.001	-0.3	-1.7
	HOMA-IR	86.4 (75.9, 97.0)	<0.001	79.6 (69.2, 90.0)	<0.001	-6.8	-7.9

Abbreviations. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOO, metabolically healthy overweight or obese; MUOO, metabolically unhealthy overweight or obese.

s% estimates are symmetric percentage differences.
All models adjusted for sex, ethnicity, age at outcome, and alcohol intake, mild and moderate exercise, educational attainment, and GHQ score in 1991/94.

Highlights

- We investigated 20-year BMI and waist circumference histories.
- Greater severity of adiposity was related to poor cardiometabolic health in normal weight and overweight/obese adults.
- The estimates for variability exposures became null upon adjustment for severity.
- Duration of central obesity was a stronger risk factor than duration of general overweight/obesity.
- Histories only partly explained the elevated disease risk factors of unhealthy groups.