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Individuals with obesity but no other metabolic risk factors are not at significantly elevated all-cause mortality risk in men and women

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What is already known about this subject

- Obesity is associated with several metabolic disorders.
- Obesity is associated with mortality risk after statistical adjustment of several risk factors.
- When Metabolic Healthy Obesity (MHO) is defined as obesity with zero or one metabolic risk factor, MHO is associated with elevated mortality risk.

What does this study adds

- MHO, defined as obesity with zero other metabolic risk factors, is not associated with increased mortality risk.
- MHO, defined as abdominal obesity with zero other metabolic risk factors, is not associated with increased mortality risk.
- Elevations in metabolic risk factors are much more strongly associated with mortality risk than obesity.

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Summary

Studies have examined mortality risk for metabolically healthy obesity, defined as zero or one metabolic risk factors but not as zero risk factors. Thus, we sought to determine the independent mortality risk associated with obesity or elevated glucose, blood pressure or lipids in isolation or clustered together. The sample included 54 089 men and women from five cohort studies (follow-up = 12.8 $\pm$ 7.2 years and 4864 [9.0%] deaths). Individuals were categorized as having obesity or elevated glucose, blood pressure or lipids alone or clustered with obesity or another metabolic factor. In our study sample, 6% of individuals presented with obesity but no other metabolic abnormalities. General obesity (hazard ratios [HR], 95% CI = 1.10, 0.8–1.6) and abdominal obesity (HR = 1.24, 0.9–1.7) in the absence of metabolic risk factors were not associated with mortality risk compared to lean individuals. Conversely, diabetes, hypertension and dyslipidaemia in isolation were significantly associated with mortality risk (HR range = 1.17–1.94, $P < 0.05$). However, when using traditional approaches, obesity (HR = 1.12, 1.02–1.23) is independently associated with mortality risk after statistical adjustment for the other metabolic risk factors. Similarly, metabolically healthy obesity, when defined as zero or one risk factor, is also associated with increased mortality risk (HR = 1.15, 1.01–1.32) as compared to lean healthy individuals. Obesity in the absence of metabolic abnormalities may not be associated with higher risk for all-cause mortality compared to lean healthy individuals. Conversely, elevation of even a single metabolic risk factor is associated with increased mortality risk.

Keywords: Body mass index, hypertension, metabolic syndrome, waist circumference.

Introduction

Obesity often presents in conjunction with several metabolic risk factors, and these factors have been independently associated with mortality risk (1–9). Current weight management guidelines recommend that all individuals with obesity should be prescribed weight loss, suggesting that obesity even without other risk factors carries health risk (10). Recently, metabolically healthy obesity has become a topic of interest, but its association with mortality risk is under debate (11–16). One of the issues with the definition of 'healthy', used in most existing studies suggesting that metabolically healthy obesity is associated with increased mortality risk, is that they may not in fact be healthy as they allow for obesity in the presence of up to one of the metabolic risk factors (11–15). This would mean that individuals with obesity and hypertension, for example, could have been categorized as healthy. The recent study by Caleyachetty *et al.* (16), which examined metabolically health obesity risk for cardiovascular events in 3.5 million adults, defined healthy as the absence of hypertension, diabetes and dyslipidaemia but did not exclude individuals with one or more preclinically elevated risk factors from being defined as healthy. This means that these 'healthy' individuals may present with the metabolic syndrome, which is also associated with increased mortality risk (17). Using the most stringent definition, wherein metabolically healthy obesity is defined as no clinical or preclinical risk factors, studies have suggested that metabolically healthy obesity would account for only 1.3% of the U.S. population (14). To our knowledge, there are no studies that examine the mortality risk for metabolically healthy obesity when defined as having no other clinical or preclinical metabolic risk factors.

Similarly, while it is clear that a clustering of metabolic risk factors with or without obesity is associated with elevated mortality risk (18, 19), a single metabolic risk factor may (20, 21) or may not (18). Previous research suggesting an independent association between risk factors and mortality has mainly used statistical adjustment for the other metabolic risk factors (1–9, 18, 20, 21) as opposed to restricting the sample to only individuals classified as healthy by the absence of risk factor(s). Sample restriction or categorization may also be the more clinically relevant approach to risk assessment but requires a very large sample size as the prevalence at which obesity and cardiometabolic risk factors occur in isolation are quite low (<10%) (22). Thus, it is unclear whether these cardiometabolic risk factors are associated with mortality risk when they occur in isolation.

To our knowledge, there has been no research examining the mortality risk associated with preclinical and clinically elevated levels of obesity, dysglycaemia, dyslipidaemia and hypertension in isolation. This research is important to understand risk stratification for treatment. Thus, the main objective of this study is to examine the association between obesity and cardiometabolic risk factors when they occur in isolation and to compare this with other commonly used approaches in the literature.

Methods

Participants

This sample includes a merged dataset from the ACLS (Updated December 31st, 2003), Coronary Artery Risk Development in Young Adults (CARDIA – Updated April 27th, 2017), Multi-Ethnic Study of Atherosclerosis (MESA – Updated November 15th, 2016) and National Health and Nutrition Examination Survey (NHANES III and continuous 1999–2008). All study participants gave their informed written consent as required by the relevant ethics boards for each survey. Institutional ethics approval to analyse this merged dataset was obtained from York University's Research Ethics Board (e2017–364).

ACLS was available through a research collaboration with study investigators. Limited data access for CARDIA and MESA was obtained through the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). This manuscript was prepared using research materials obtained from the NHLBI Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the study survey investigators or the NHLBI. NHANES is available publicly online.

The initial merged dataset contained 129 915 participants with complete mortality follow-up data. Participants were included if they were over 18 years of age (n = 114 956) and had information on age, gender, body mass index (BMI), ethnicity and smoking status (n = 78 664) and information for all of the risk factors (BMI, waist, glucose, systolic blood pressure [SBP], diastolic blood pressure [DBP], high-density lipoprotein [HDL] and triglycerides) (n = 54 857). Participants were excluded if they had a BMI less than 18.5 kg m^{-2}, leaving a final sample of 54 089 individuals with complete baseline and mortality follow-up data.

Datasets

Aerobics Center Longitudinal Study (ACLS) includes a cohort of participants who attended the Cooper Clinic (Dallas, TX) for periodic self- or physician-referred medical examinations between 1987 and 2001. Mortality follow-up till December 31, 2003 was used in this analysis.

Coronary Artery Risk Development in Young Adults (CARDIA) is a multicentre, longitudinal study conducted in 1985–1986 on 5115 participants aged 18–20 years from Birmingham, AL; Chicago, IL; Minneapolis, MN; and

Oakland, CA (23). Mortality follow-up till December 31, 2011 was used in this analysis.

Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study of 6800 ethnically diverse (White, Black, Hispanic and Asian) men and women beginning in 1999. Participants were followed up every 9–12 months to ascertain medical events and mortality status through to examination 5 (August 2015) was used for these analyses. Mortality status was confirmed using medical records, death certificates, interviews, questionnaires and other procedures (24).

National Health and Nutrition Examination Survey (NHANES) III and Continuous are a series of nationally representative cross-sectional surveys collected using a stratified, multistage, probability cluster design. NHANES III was conducted between 1988 and 1994 on 33 994 persons, aged 2 months and older. NHANES continuous cycles are released biannually, with 1999–2000 (n = 9965), 2001–2002 (n = 11 039), 2003–2004 (n = 10 122), 2005–2006 (n = 9950) and 2007–2008 (n = 9762) included in these analyses. Public access Mortality Linkage data file with follow-up through December 31st, 2011 was used for these analyses.

Survey methods

Age, gender, ethnicity (White or other), smoking status (non or current), self-reported medical history and medications were assessed by questionnaire. BMI (kg m^{-2}) was calculated from measured weight and height. Standard BMI cut-offs for normal weight (NW: 18.5 to 24.9 kg m^{-2}), overweight (OW: 25 to 29.9 kg m^{-2}) and obese (OB: ≥30 kg m^{-2}) were used. Waist circumference (WC) was assessed by trained technicians.

Obesity and metabolic factor measurements

The following cut-off points were used to classify factors into low, moderate and higher risk categories using standard Normal, Preclinical and Clinical cut-offs, respectively (Table 1) (25, 26). The 'No RF' group was defined as being low risk for all other metabolic risk factor categories and was free of obesity. Hypertension was categorized as exceeding the clinical cut-offs for blood pressure, as given in Table 1. Diabetes was categorized as exceeding the clinical cut-offs for glucose, as given in Table 1. Dyslipidaemia was categorized as exceeding the clinical cut-offs for HDL and triglycerides, as given in Table 1.

Statistical analysis

Generalized linear mixed models (Proc Glimmix, SAS v9.4, Cary, NC) were used to examine differences in means and prevalence. Cox proportional hazards regression was used to estimate hazard ratios (HR) to examine differences in all-cause mortality across metabolic risk groups adjusted for age, gender, smoking status and ethnicity. For each model, the groups were divided into healthy, preclinical and clinically elevated risk factors according to BMI, glucose, blood pressure or lipids and were then further divided into the presence or absence of the other risk factors, with the healthy–no risk factors (lowest risk) category being the referent group (HR = 1.00). Proportionality assumptions for the mortality analyses were assessed using graphical methods. All analyses allowed for random intercepts to account for variation between study samples.

To allow for comparisons with previous studies, two sets of analyses were conducted. First, the relationship between metabolic factors and mortality was assessed when metabolically healthy was defined as having zero or only one risk factor, with men and women collapsed while adjusting for age, smoking status, ethnicity and follow-up time. Second, a single model examining the independent associations between high-risk glucose, lipids, blood pressure and obesity was conducted. Statistical significance was set at alpha = 0.05.

Results

Characteristics of participants stratified by risk profile are shown in Table 2. Within the entire sample, 16.7% of participants were free from all preclinical or clinical metabolic abnormalities and obesity, while 52.0% of the sample had more than one metabolic risk factor or obesity. Among those with obesity, 5.8% of individuals did not present with any other risk factors. Participants who were classified as having one preclinical or clinical risk factor (i.e. glucose, blood pressure or lipid) or obesity alone ranged from 1.2 to 21.7%. During the 12.8 ± 7.2-year follow-up, there were 4864 (9.0%) deaths. The NoRF and Obesity Only groups tended to be younger and had the lowest incidences of death of all groups.

The associations between obesity, metabolic status and mortality risk are shown in Fig. 1. Obesity (HR, 95% CI = 1.10, 0.8–1.6) without other metabolic risk factors was not associated with increased mortality risk as compared to lean healthy individuals, but obesity was associated with higher risk for mortality when in combination with at least one other factor (HR range: 1.33–1.80, $P < 0.05$, Fig. 1) as compared to lean healthy individuals. In contrast, diabetes (HR = 1.94, 1.2–3.1), preclinical hypertension (HR = 1.36, 1.1–1.7), hypertension (HR = 1.64, 1.4–1.9) and dyslipidaemia (HR = 1.17, 1.0–1.3) alone were associated with increased HR of all-cause mortality as compared to their healthy counterparts. Furthermore, the mortality risk for these metabolic factors in combination with other factors mortality risk was even higher (HR range: 1.22–2.58, $P < 0.05$). When obesity was defined using WC, abdominal obesity alone was also not significantly

Table 1 Normal, preclinical and clinical cut-offs for obesity, blood pressure, glucose and lipids

Factors	Normal	Preclinical	Clinical
Obesity	BMI: 18.5–24.9 kg m^{-2}	BMI: 25–29.9 kg m^{-2}	BMI ≥ 30 kg m^{-2}
Ab obesity	WC: <80 cm (♀)	WC: 80–87.9 cm (♀)	WC: ≥88 cm (♀)
	WC: <94 cm (♂)	WC: 94–101.9 cm (♂)	WC: ≤102 cm (♂)
Blood pressure	SBP < 130 mmHg	SBP: 130–139 mmHg	SBP ≥ 140 mmHg
			DBP ≥ 90 mmHg
			BP meds, or
	DBP < 85 mmHg	DBP: 85–89 mmHg	SR hypertension
Glucose	Glucose < 5.6 mM	Glucose: 5.6–6.9 mM	Glucose ≥ 7 mM
			T2D meds, or
			SR diabetes
Lipids	Trig: <1.69 mM	Trig: 1.69–2.25 mM	Trig ≥ 2.26 mM
			Chol ≥ 6.2 mM
			Lipid meds, or
	HDL ≥ 1.29 mM (♀)	HDL < 1.29 mM (♀)	SR hyperlipidaemia
	HDL ≥ 1.04 mM (♂)	HDL < 1.04 mM (♂)	
	Chol: <5.2 mM	Chol: 5.2–6.1 mM	

BMI, body mass index; DBP, diastolic blood pressure; Chol, cholesterol; HDL: high density lipoprotein; SBP, systolic blood pressure; SR, self-report; T2D, type 2 diabetes; Trig, triglycerides; meds, medications; WC, waist circumference.

associated with mortality (HR = 1.24, 0.9–1.7, $P = 0.16$, Fig. 2) as compared to healthy low-waist individuals.

When metabolically healthy was defined as zero or one metabolic risk factor as done in previous research, metabolically healthy obesity was associated with increased mortality risk as compared to healthy lean (HR = 1.15, 1.01–1.32). In a model with all of the risk factors, obesity (HR = 1.12, 1.02–1.23), diabetes (HR = 1.13, 1.05–1.21), hypertension (HR = 1.21, 1.12–1.32) and dyslipidaemia (HR = 1.17, 1.07–1.28) were independently associated with all-cause mortality.

Discussion

Results of this analysis illustrate that obesity in the absence of metabolic risk factors may not be associated with higher mortality risk than lean healthy individuals. This is in contrast to previous studies that have suggested that obesity is independently associated with mortality risk (14, 15, 27, 28). These differences may, in part, be related to how metabolically 'healthy' has been defined in the past due to constraints related to sample size as obesity in the absence of other metabolic risk factors is rare (14). In contrast with obesity, we observe that other common metabolic risk factors in isolation are associated with all-cause mortality risk.

In the literature, the association between obesity and mortality risk independent of commonly observed comorbidities such as diabetes, hypertension or dyslipidaemia is most commonly demonstrated using a single model with statistical adjustment for the other health risk factors as continuous variables in the same model (18–21, 29, 30) or as categorical variables (High and low risk) (20, 21, 29, 30). When we used statistical adjustment, we also observe that obesity, hypertension, dyslipidaemia and diabetes were all independently associated with mortality risk. When

Table 2 Characteristics of participants by metabolic status group

Variable	No RF Mean (SE)	Obesity only Mean (SE)	Glucose only Mean (SE)	BP only Mean (SE)	Dyslipidaemia only Mean (SE)	Multiple RF Mean (SE)
N	9 018	656	1 702	2 891	11 712	28 110
Age (years)	40.2 (5.3)	39.6 (5.3)	44.6 (5.3)*	48.1 (5.3)*	42.5 (5.3)*	49.6 (5.3)*
Gender (% M)	45.0 (6.2)	43.7 (6.4)	58.0 (6.2)*	59.1 (6.2)*	48.9 (6.2)*	59.5 (6.1)*
White (%)	56.4 (10.9)	42.3 (10.9)*	54.6 (10.9)*	54.9 (10.9)*	57.6 (10.9)*	54.9 (10.9)*
Smoker (%)	20.8 (3.0)	18.5 (3.3)	18.9 (3.1)	18.7 (3.0)*	25.1 (3.0)*	22.0 (2.9)*
Waist (M-cm)	86.4 (2.2)	107.2 (2.3)*	89.1 (2.2)*	89.5 (2.2)*	90.7 (2.2)*	99.5 (2.2)*
Waist (F-cm)	77.7 (3.6)	98.9 (3.6)*	80.6 (3.6)*	81.1 (3.6)*	81.2 (3.6)*	95.1 (3.6)*
Death (%)	6.6 (4.5)	4.9 (4.7)	10.8 (4.6)*	14.1 (4.6)*	8.4 (4.5)*	16.3 (4.5)*
Follow-up (years)	14.2 (3.1)	14.4 (3.1)	13.9 (3.1)*	13.3 (3.1)*	15.2 (3.1)*	13.9 (3.1)*

*Significantly different from NoRF ($P < 0.05$).
F, female; M, male; RF, risk factor.

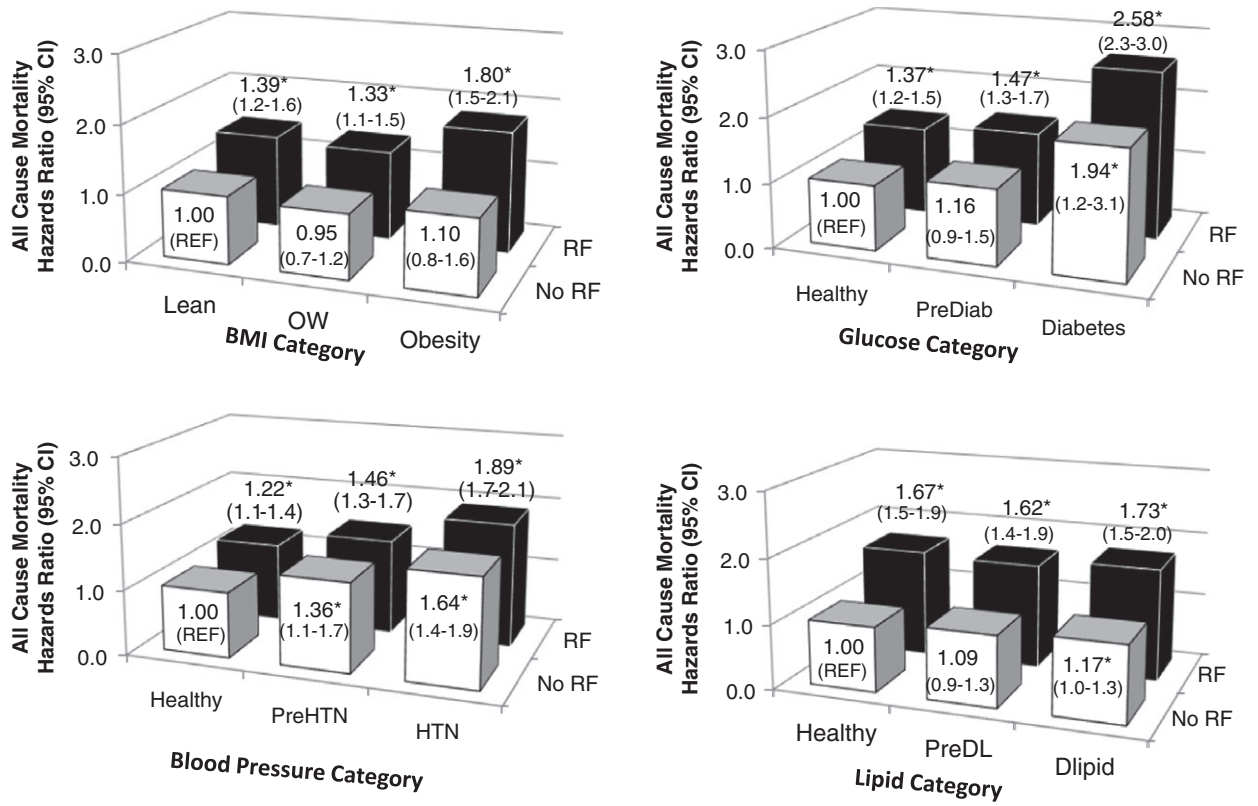

Figure 1 Hazards ratio of all-cause mortality by health status. *HR significantly different from No RF (Referent, $P < 0.05$). Figures are adjusted for age, gender, white ethnicity, smoking status and follow-up time. No RF = low risk for the other metabolic variables and no obesity. RF = at least one additional preclinical or clinical metabolic risk factor or obesity (Table 1). Dlipid, dyslipidaemia; HTN, hypertension; OW, overweight; PreDiab, preclinical diabetes; PreDL, preclinical Dyslipidaemia; PreHTN, preclinical hypertension.

using the stratified analysis, which is more akin to risk stratification approaches in clinical care, we demonstrate that the metabolic variables in isolation, but not obesity, were associated with all-cause mortality as compared to their healthy counterparts. We also demonstrate that preclinically elevated risk factors in isolation were not associated with mortality risk with the exception of pre-hypertension. This is in line with the metabolic syndrome concept (17) in that the clustering of preclinical risk factors is associated with increased risk.

A systematic review and meta-analysis by Kramer *et al.* (15) report that metabolically healthy obesity is associated with increased mortality risk. However, one of the major limitations of our previous work and other published research on metabolically healthy obesity is that individuals with obesity and one (or more) metabolic risk factor(s) were still considered healthy (11–15). This is clearly problematic as the current study demonstrates that diabetes, dyslipidaemia, hypertension and even pre-hypertension in isolation are associated with increased mortality risk. Thus, allowing for individuals with risk factors to be included in the definition of healthy may have incorrectly inflated the mortality risk associated with this group.

Previous studies have reported that metabolically healthy obesity, defined as no risk factors, may be as low as 0.4% (22), and thus, those studies may have elected to use this more lenient definition of healthy due to sample size issues. In our study, only 1.2% of individuals presented with obesity and remained free of all clinical and preclinical risk factors. Thus, this study with over 50 000 individuals and nearly 5000 mortality events represents one of the first few sufficiently large studies to date to properly examine mortality risk in metabolically healthy obesity. In contrast to previous research, we demonstrate that obesity alone, without the presence of other preclinical or clinical metabolic risk factors, is not associated with elevated mortality risk in men or women. It is suggested by others (15) that individuals with metabolically healthy obesity are at increased mortality risk as they are more likely than their normal-weight counterparts to transition to unhealthy over time. Our study used a single risk assessment, and changes in obesity and the risk profile over the 13 year follow-up were not captured. However, changes in metabolic status would theoretically elevate the mortality risk with the metabolic healthy obesity group. That we saw no differences in mortality risk by BMI in the healthy group may suggest that the true mortality risk

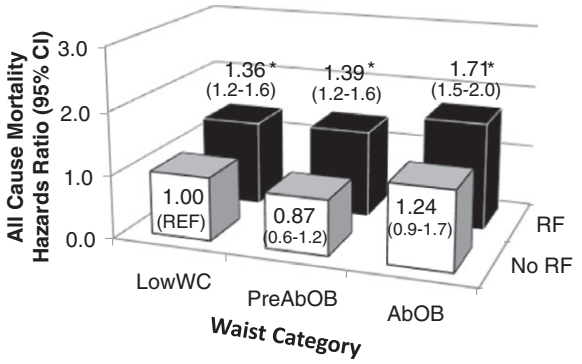

Figure 2 Association between waist circumference and metabolic status and all-cause mortality risk. *HR significantly different from No RF (Referent, $P < 0.05$). Figures are adjusted for age, gender, white ethnicity, smoking status and follow-up time. No RF = low risk for the metabolic variables. RF = at least one additional preclinical or clinical metabolic risk factor. PreAbOB = preclinical abdominal obesity (Men: waist circumference: 94–101.9 cm; Women: waist circumference: 80–87.9 cm). AbOB = abdominal obesity (Men: waist circumference: ≥102 cm; Women: waist circumference: ≥88 cm).

for the metabolically healthy obesity group that remains free of metabolic risk factors over time could be lower than what we report: the obesity paradox (31).

Diabetes, dyslipidaemia and hypertension have been widely accepted and regularly reviewed clinical criteria and cut-offs for diagnosis. However, obesity has only been recently recognized as a chronic disease by the World Health Organization (32) and the American Medical Association (33). This change acknowledges the unique aetiology and health consequences of obesity that necessitates the development of appropriate medical interventions and treatments. In these reports, obesity is generally described as the presence of abnormal or excess body fat that impairs health (33). However, many current weight management guidelines do not make the distinction between excess body fat that does or does not impair health and simply diagnose obesity using a BMI greater than or equal to 30 kg m^{-2}. There is much research suggesting that the deleterious effects of obesity are more closely associated with abdominal obesity (34). However, even when using WC, the association between obesity and mortality risk remained non-significant, and the magnitude of the risk estimates were not substantially different using WC *versus* BMI. Thus, whether abdominal obesity should be central to risk criteria, such as some metabolic syndrome criteria (35) or the hypertriglyceridemic waist (36), is unclear.

Current clinical weight management guidelines prescribe weight loss for all individuals with obesity as defined by a BMI > 30 kg m^{-2} regardless of their metabolic status (10). If the deleterious effects of obesity occur predominantly through changes in these other metabolic risk factors, then this would support risk algorithms such as the Edmonton Obesity Staging System, which suggest a triaged approach that only recommends weight loss for individuals with obesity who have physical, functional, or psychological obesity-related comorbidities (37). However, if abdominal or overall obesity does carry independent risk, then this would support current guidelines suggesting that weight loss should be recommended for all individuals with obesity regardless of their health profile (38). In our study sample, 6% of individuals with obesity presented without any other risk factors and were not at significantly elevated mortality risk as compared to healthy lean individuals. Thus, it is unclear whether these individuals with metabolically healthy obesity would benefit from weight loss. Furthermore, given the low success rates for obesity reduction (39, 40) and the stigma and bias experienced by those struggling with obesity (41), it may be particularly important to confirm whether obesity itself is associated with increased morbidity and mortality risk or reduced quality of life outcomes. Furthermore, whether metabolically healthy individuals with obesity benefit from weight loss in terms of physical, functional, psychological and metabolic outcomes needs to be confirmed in future research.

The strengths and limitations of this study warrant mention. First, this study uses a harmonized sample from five separate well-established cohort studies. With this large sample, we were able to examine the mortality risk associated with obesity, glucose, blood pressure and lipids in isolation or clustered together. Although the methods used between studies were not identical and were conducted over a long time span, they did use standardized and clinically accepted methodologies for the measures used here, and the statistical analyses used accommodated for some of the potential differences between the studies. However, socioeconomic status, medications, physical activity and diet were not consistently captured between surveys and may have confounded results observed. It is unclear whether individuals with metabolically healthy obesity also had better lifestyle factors, higher socioeconomic status, better medical care or other factors that may have confounded the results. Although the models were adjusted for white ethnicity, we did not examine other ethnicities as it was not always captured in a way that would allow us to use ethnic-specific guidelines for obesity or metabolic risk factors. Finally, this study was limited to the examination of all-cause mortality, and it may be expected that the associations may be stronger with cardiovascular disease mortality or quality of life measures.

Summary

In conclusion, we suggest that obesity in the *absence* of metabolic abnormalities is not associated with increased risk for all-cause mortality as compared to normal weight individuals. In contrast, diabetes, hypertension and

dyslipidaemia in isolation and in combination are more strongly associated with increased mortality risk.

Author contributions

Each author made substantial contributions to conception and design. JLK and MR were responsible for the analysis and interpretation of data. All authors were involved in revising the manuscript critically for important intellectual content and gave final approval of the version to be published. Each author takes responsibility for the content and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest Statement

No conflict of interest was declared.

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