New Metabolic Health Definition Might Not Be a Reliable Predictor for Mortality in the Nonobese Chinese Population

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Research Article

Keywords: All-cause mortality, Metabolic health, non-obese individuals

Posted Date: November 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1071767/v1>

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Abstract

Background

A new metabolic health (MH) definition was proposed recently. We aimed to investigate the association between the new MH definition and all-cause mortality (ACM) in a nonobese Chinese population.

Methods

A total of 1157 participants with 15-year of follow-up were included for the present analysis. The association between MH and ACM were analyzed by Cox regression models with overlap weighting according to propensity score (PS) as primary analysis.

Results

At baseline, 920 (79.5%) participants were categorized as MH and 237 (20.5%) participants were categorized as metabolic unhealth (MUH) by this new definition. During follow-up, ACM occurred in 30 participants with mortality rate at 1.85% in MH group and 5.49% in MUH group, respectively. In the crude sample, Kaplan-Meier (K-M) analysis demonstrated a significantly lower ACM in MH group when compared to MUH group (log-rank $p = 0.002$). However, in multivariable Cox analysis, MH was not significantly associated with reduced ACM when compared to MUH with HR at 0.92 (95% CI: 0.32-2.64, $p = 0.875$). Moreover, overlap weighting-adjusted K-M analysis showed that the cumulative incidence of ACM was not significantly different between MH and MUH groups (adjusted $p = 0.589$). In the primary multivariable Cox analysis with overlap weighting, the HR for ACM was 0.70 (95% CI: 0.24-2.06, $p = 0.519$) in MH group in reference to MUH group. Additional PS analyses yielded similar results.

Conclusion

The new MH definition was not significantly associated with ACM in non-obese Chinese people. Further investigations are needed.

Background

Previous studies investigating the effects of metabolically healthy obesity (MHO) on morbidity and mortality have yielded contradictory results [1–4]. The absence of metabolic syndrome and its components or absence of insulin resistance were widely used to identify metabolic health (MH)[5, 6]. The inconsistency of results in those literatures that some obese participants without metabolic syndrome at baseline were still at increased risk of cardiovascular events and total death[2–4] indicated the insufficiency of those previous definitions and criteria to define MH. Recently, a new definition of MH has been proposed by Zembic et al based on the data from the third National Health and Nutrition

Examination Survey (NHANES-III) and validated in UK biobank cohort[7]. It was shown that the new definition was not only able to stratify risk of mortality in people with obesity, but also in people with overweight and normal weight.

For nonobese individuals, they can also exhibit abnormal metabolic profiles, resulting in greater risk of adverse clinical outcomes[8–10]. Unfortunately, nonobese individuals have not been focused with regards to the prevention of cardiometabolic diseases more commonly related to obesity. Therefore, identification of those individuals at high risk is important and meaningful. As we mentioned before, the new MH definition was mainly derived from NHANES-III cohort, while Asian populations were underrepresented. In this study, we aimed to investigate the clinical significance of the new defined MH for all-cause mortality (ACM) in a nonobese Chinese population.

Methods

Study population

In 1992, a group of 1450 individuals received health survey in an urban community of Chengdu, Sichuan province, China. In 2007, we conducted another health survey on the same group of participants. The two surveys were supported by a project from the National Eighth Five-Year Research Plan and megaprojects of science research for China's 11th 5-year plan, respectively. Among the 1450 individuals, 711 individuals received an interview health survey in 2007, and telephone follow-ups were conducted for the remaining individuals ($n = 518$). After excluding the individuals who were lost to follow-up and the obese individuals, a total of 1157 nonobese participants with complete data were analyzed (figure 1). Other detailed information of these participants has been reported elsewhere[11–13].

The surveys were approved by the Ministry of Health of China, as well as by the Ethics Committee of West China Hospital of Sichuan University. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. All participants provided written informed consent.

Data collection

At baseline, the survey content included standardized questionnaire, anthropometric measurements, and laboratory tests. Standardized questionnaire collected the information on demographic characteristics. Based on the standard methods[14], we performed anthropometric measurements, which included blood pressure (BP), height, weight, waist circumference (WC), hip circumference (HC) and so on. Laboratory tests consisted of fasting plasma glucose (FPG) and fasting lipid profiles, including triglycerides (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C).

Related definitions

According to the original study, the criteria for the new MH definition are as follows: 1) systolic blood pressure (SBP) less than 130 mmHg and without antihypertensive drugs, 2) waist to hip ratio (WHR) less

than 0.95 for women and less than 1.03 for men, 3) no prevalent diabetes[7].

Other definitions used in the study were as follows. Cardiovascular diseases (CVD) were defined as self-reported coronary heart disease and/or cerebral stroke. Diabetes was defined by self-reported history or $\text{FPG} \geq 7.0 \text{ mmol/L}$. WHR was calculated as follows: $\text{WHR} = \text{WC}/\text{HC}$. BMI was calculated as follows: $\text{BMI} = \text{Weight (Kg)}/\text{Height}^2 (\text{m}^2)$. Smoking was categorized as never, current and past. Alcohol intake was defined as average intake of alcohol $\geq 50 \text{ g/day}$. Physical activity was defined as exercise one or more times per week, at least 20 minutes for each time[11–13].

Endpoint

The primary end point was ACM from study baseline in 1992 to follow-up in 2007. The occurrence of ACM was confirmed via telephone contact with referring relatives.

Statistical analysis

For summarizing baseline characteristics of subjects, continuous variables were presented as mean $\pm$ standard deviation (SD) and median with interquartile range (IQR) where appropriate, and categorical variables as number (percentage) for each group.

Given the observational nature of the present study, propensity scores (PS) were developed to account for potential confounding by observed baseline characteristics. PS methods replace an entire set of baseline characteristics with a single composite score, and this can be accomplished with a number of potential confounders in excess of what is possible with conventional regression methods[15, 16]. The individual propensities for diagnosis of MH were estimated with the use of a multivariable logistic-regression model that included the following covariates, including age, sex, smoking, drinking, exercise, CVD, diastolic blood pressure (DBP), TC, HDL-C, LDL-C, TG and BMI. Then, associations between MH and ACM were estimated by Cox regression models with the use of three PS methods, including overlap weighting, propensity-score matching (PSM), and the PS as an additional covariate.

Overlap weighting was chosen as the primary method for confounder adjustment in this study, because it could minimize the influence of extreme PS on model output [17]. Overlap weighting could assign weights to each patient that are proportional to the probability of that patient belonging to the opposite exposed group. Specifically, exposed patients are weighted by the unexposed probability ($1 - \text{PS}$) and unexposed patients are weighted by the exposed probability (PS). Overlap weighting assigns greater weight to patients in which treatment cannot be predicted and lesser weight to patients with extreme PS (approaching 0.0 or 1.0) preventing outliers from dominating the analysis and decreasing precision, which is a concern with inverse probability weighting[18]. Furthermore, overlap weighting has the favorable property of resulting in the exact balance (absolute standardized differences [ASD] = 0) of all variables included in the multivariable logistic regression model used to derive the PS. PSM was also used to adjust for clinically relevant baseline characteristics that were potentially confounding variables, and patients were matched 1:1 using the nearest neighbor method, with a fixed caliper width of 0.08. After overlap weighting and PSM, ASD were estimated for the baseline covariates before and after the

processes to assess prematch imbalance and postmatch balance, and ASD of less than 0.1 for a given covariate indicate a relatively small imbalance[19]. In addition, cumulative hazard plots were also produced to display the cumulative incidence of ACM in different methods.

The statistical analyses were performed with the use of R software, version 4.1.0 (R Project for Statistical Computing). For all statistical analyses, a two-sided p value of 0.050 was considered statistically significant.

Results

Baseline characteristics

In total, 1157 nonobese subjects with complete data were included for the present analysis. Baseline characteristics for the crude sample and for individuals with MH and with MUH are shown in Table 1. There were 920 individuals in MH group and 237 individuals in MUH group. Compared to participants with MUH, participants with MH were younger, more likely to have a lower weight, BMI, SBP, DBP, WC, HC, TG, TG, LDL-C and FPG. In addition, the MH group was characterized by a greater portion of female and lower portion of drinking and exercise.

Table 1
Baseline characteristics of crude sample.

Variables	Crude sample (n = 1157)		
	MUH (n = 237)	MH (n = 920)	Absolute standardized difference
Sex (female)	73 (30.8)	343 (37.3)	0.137
Age (years)	51.00 (47.00, 55.00)	48.00 (43.00, 52.00)	0.544
Smoking			0.238
never	140 (59.1)	506 (55.0)	
previous	14 (5.9)	19 (2.1)	
current	83 (35.0)	395 (42.9)	
Drinking	44 (18.6)	119 (12.9)	0.155
Exercise	65 (27.4)	211 (22.9)	0.104
CVD	5 (2.1)	15 (1.6)	0.035
DBP (mmHg)	86.00 (78.00, 90.00)	70.00 (68.00, 75.00)	1.523
TC (mmol/L)	4.60 (4.10, 5.10)	4.30 (3.90, 4.80)	0.275
LDL-C (mmol/L)	2.30 (1.70, 2.90)	2.20 (1.70, 2.70)	0.120
HDL-C (mmol/L)	1.30 (1.10, 1.50)	1.30 (1.10, 1.40)	0.053
TG (mmol/L)	2.10 (1.60, 2.50)	1.80 (1.50, 2.40)	0.281
Height (cm)	162.00 (157.00, 167.00)	161.50 (156.00, 167.00)	0.043
Weight (kg)	62.00 (57.00, 68.00)	59.00 (53.60, 65.00)	0.384
BMI (kg/m ²)	23.90 (22.20, 25.80)	22.70 (21.00, 24.60)	0.462
Elements of new MH definition			

Values are median (IQR) or n (%).

Abbreviations: PSM = propensity score matching, MUH = metabolically unhealthy, MH = metabolically healthy, CVD = cardiovascular diseases, DBP = diastolic blood pressure, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, TG = triglyceride, BMI = body mass index, SBP = systolic blood pressure, FPG= fasting plasma glucose

Variables	Crude sample (n = 1157)		
	MUH (n = 237)	MH (n = 920)	Absolute standardized difference
SBP (mmHg)	135.00 (130.00, 146.00)	110.00 (100.00, 118.00)	1.903
waist (cm)	79.00 (73.00, 84.00)	75.00 (70.00, 80.00)	0.463
hip (cm)	93.00 (89.00, 96.00)	91.00 (87.00, 94.00)	0.325
FPG (mmol/L)	4.50 (4.00, 5.40)	4.20 (3.80, 4.70)	0.335
Values are median (IQR) or n (%).			
Abbreviations: PSM = propensity score matching, MUH = metabolically unhealthy, MH = metabolically healthy, CVD = cardiovascular diseases, DBP = diastolic blood pressure, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, TG = triglyceride, BMI = body mass index, SBP = systolic blood pressure, FPG= fasting plasma glucose			

The β coefficients for MH according to all the variables included in PS model are presented in Table S1. The C-statistic for the PS model was 0.88. As shown in figure 2A, prior to weighting and matching, lesser overlap of PS curves of the two groups (MH vs MUH) indicates a greater risk of confounding. After overlap weighting, the overall distribution of the estimated PS for ACM in the cohort was balanced (figure 2B). For each variable, ASD for all characteristic was < 0.1 after overlap weighting. Both indicated that the matched population in the 2 groups was subsequently comparable (Table 2). After PSM, PS curves for MH and MUH were superimposed, indicating that the baseline differences between MH and MUH were largely attenuated (Figure 2C). In PSM cohort, ASD for most characteristics was < 0.1, except age, DBP, TC and LDL-C (Table 2).

Table 2
Baseline characteristics of overlap weighted sample and propensity score matched sample.

Variables	After overlap weighting			After PSM (n = 264)		
	MUH	MH	Absolute standardized difference	MUH (n = 132)	MH (n = 132)	Absolute standardized difference
Sex (female)	33.7 (32.1)	33.7 (32.1)	<0.001	42 (31.8)	44 (33.3)	0.032
Age (years)	49.00 (45.40, 54.00)	50.00 (46.00, 54.00)	<0.001	49.00 (46.00, 55.00)	50.00 (45.75, 54.00)	0.140
Smoking			<0.001			0.075
never	57.4 (54.7)	57.4 (54.7)		72 (54.5)	72 (54.5)	
previous	4.0 (3.8)	4.0 (3.8)		5 (3.8)	7 (5.3)	
current	43.6 (41.5)	43.6 (41.5)		55 (41.7)	53 (40.2)	
Drinking	18.1 (17.2)	18.1 (17.2)	<0.001	23 (17.4)	27 (20.5)	0.077
Exercise	27.9 (26.6)	27.9 (26.6)	<0.001	32 (24.2)	27 (20.5)	0.091
CVD	2.9 (2.8)	2.9 (2.8)	<0.001	3 (2.3)	5 (3.8)	0.088
DBP (mmHg)	79.08 (70.00, 80.61)	78.00 (73.00, 80.00)	<0.001	80.00 (70.75, 80.00)	80.00 (72.00, 80.00)	0.132
TC (mmol/L)	4.50 (4.10, 5.00)	4.50 (4.00, 5.00)	<0.001	4.50 (4.10, 5.00)	4.50 (4.10, 5.00)	0.152
LDL-C (mmol/L)	2.30 (1.70, 2.90)	2.30 (1.70, 2.70)	<0.001	2.25 (1.60, 2.80)	2.30 (1.80, 2.82)	0.127
HDL-C (mmol/L)	1.20 (1.00, 1.40)	1.20 (1.10, 1.40)	<0.001	1.20 (1.00, 1.40)	1.20 (1.10, 1.40)	0.088
TG (mmol/L)	2.00 (1.60, 2.50)	2.00 (1.60, 2.60)	<0.001	2.00 (1.60, 2.62)	2.00 (1.60, 2.70)	0.041

Values are median (IQR) or n (%), and abbreviations as in Table 1.

Variables	After overlap weighting			After PSM (n = 264)		
	MUH	MH	Absolute standardized difference	MUH (n = 132)	MH (n = 132)	Absolute standardized difference
Height (cm)	162.00 (157.00, 166.98)	162.00 (157.00, 168.00)	0.067	161.00 (157.00, 166.00)	162.00 (156.75, 168.00)	0.065
Weight (kg)	61.84 (55.00, 66.63)	62.00 (56.00, 67.00)	0.042	61.00 (55.75, 66.00)	62.00 (55.75, 67.00)	0.012
BMI (kg/m ²)	23.47 (21.80, 25.70)	23.60 (21.80, 25.10)	<0.001	23.50 (21.80, 25.63)	23.60 (21.60, 25.10)	0.034
Values are median (IQR) or n (%), and abbreviations as in Table 1.						

Survival analysis

During follow-up time, ACM occurred in 30 participants. Among them, there were 5 cancer related death and 2 stroke related death. The cause of death could not be confirmed in 23 participants. The ACM rate was 1.85% (n = 17) in MH group and 5.49% (n = 13) in MUH group, respectively. Figure 3A depicts the Kaplan-Meier (K-M) curves for ACM in the crude sample, and the cumulative incidence of ACM is significantly lower in participants with MH when compared to those with MUH (log-rank p = 0.002). In the crude analysis, individuals with MH were less likely to have had a primary endpoint event than those with MUH (HR: 0.33, 95% CI: 0.16-0.68, p = 0.003) (Table 3). After adjusting for potential confounding factors, including age, sex, smoking, drinking, exercise, CVD, DBP, TC, HDL-C, TG, LDL-C and BMI, HR was 0.92 (95% CI: 0.32-2.64, p = 0.875). For including many covariates, the convergence of the model may be poor, and the results were exploratory.

Table 3

Associations between MH and all-cause mortality in the crude analysis, multivariable analysis and propensity-score analyses.

Analysis	ACM
No. of events/no. of patients at risk (%) *	
MH	17/920 (1.85%)
MUH	13/237 (5.49%)
Crude analysis	0.33 (0.16, 0.68), 0.003
Propensity-score analyses	
With overlap weighting (univariable)	0.69 (0.24, 1.99), 0.489
With overlap weighting (multivariable) †	0.70 (0.24, 2.06), 0.519
With PSM (univariable)	1.00 (0.25, 4.00), 0.999
With PSM (multivariable) ‡	1.12 (0.27, 4.56), 0.875
Adjusted for PS §	0.84 (0.28, 2.58), 0.766
Adjusted for PS	0.86 (0.29, 2.57), 0.790
Multivariable analysis ¶	0.92 (0.32, 2.64), 0.875
Values are n (%) or HRs (95% CI) with p values.	
* Binary event rates.	
For the relatively small number of ACM, multivariable models only adjusted for some basic variables to ensure the convergence of the model: † adjustment for age and sex; ‡ adjustment for age, sex, DBP, TC and HDL-C; § adjustment for propensity score; adjustment for propensity score plus age and sex.	
¶ Adjustment for age, sex, smoking, drinking, exercise, CVD, DBP, TC, HDL-C, TG, LDL-C and BMI; for including many covariates, the convergence of the model may be poor, and the results were exploratory.	
Abbreviations: ACM = all-cause mortality, HRs = HR = hazard ratios, CI = confidence interval, and other abbreviations as in Table 1.	

Overlap weighting-adjusted K-M analysis showed that the cumulative incidence of ACM is not significantly different between participants with MH or MUH (adjusted $p = 0.589$) (Figure 3B). In the primary univariable and multivariable Cox regression analysis with overlap weighting, no significant association between MH and ACM was revealed. The HRs were 0.69 (95% CI: 0.24-1.99, $p = 0.489$) and 0.70 (95% CI: 0.24-2.06, $p = 0.519$), respectively (Table 3). Additional PS analyses yielded similar results. No significant difference in cumulative ACM was observed between MH and MUH subgroups in PSM cohort (log-rank $p = 1.000$) (Figure 3C). Both univariable (HR: 1.00, 95% CI: 0.25-4.00, $p = 0.999$) and multivariable (HR: 1.11, 95% CI: 0.27-4.51, $p = 0.887$) PSM Cox models showed that MH was not associated with decreased mortality. In the last, after including PS as another covariate, the results

remained the same with HR at 0.84 (95% CI: 0.28-2.58, $p = 0.766$) and 0.86 (95% CI: 0.32-2.64, $p = 0.875$) in the univariable and multivariable analyses, respectively (Table 3).

Discussion

In this analysis involving a nonobese Chinese population, the risk of ACM was not significantly different among individuals who were classified as MH and MUH by this new definition. The results indicated that this new MH definition might not be suitable for mortality risk stratification for nonobese Chinese people. Further studies are needed to explore the role of this new MH definition in larger populations.

Despite the general association between obesity and its co-morbidities, there are individuals who are normal-to over-weight but having abnormal metabolic profiles, namely the metabolically unhealthy non-obese (MUNO) or metabolically obese normal-weight (MONW) phenotype [20–23]. It was demonstrated that individuals with MONW/MUNO were at higher risk of increased arterial stiffness and carotid atherosclerosis[21], stroke[22, 23], as well as higher risk of ACM and cardiovascular mortality[24, 25], when compared to MHO. Those findings highlight that it maybe the abnormal metabolic profile, rather than obesity defined by BMI, placing individuals at increased risk for cardiovascular diseases and mortality. Therefore, screening for metabolic risk factors in non-obese but unhealthy individuals should be emphasized.

A meta-analysis showed that the prevalence of MONW around the world varies largely, ranging from 6.6–45.9%[26]. This heterogeneity was affected by several factors, including participants' age, gender, ethnicities, region, sample size, MONW criteria (criteria for obesity and metabolically healthy) and so on. A recent study demonstrated that the overall prevalence of MONW was 16.1% in a general Chinese population [27]. In this study, individuals were considered as MONW if they had at least two metabolically abnormal trait based on the metabolic syndrome criteria from the International Diabetes Federation in 2015 and BMI of 18.5-23.9 kg/m². While a more previous study showed that the prevalence of MONW was as low as 4.3% in a Chinese Beijing urban cohort[28]. In this study, MONW was defined as BMI of 18.5-25 kg/m² and metabolic abnormality referenced at least 3 abnormal traits among the factors of BP, WC, TG, FPG, and HDL-C. In our present study, according to the new MH definition, the prevalence of MUNO was 20.5%. As we can see, there are various criteria to evaluate MUNO/MONW currently, no consensus has been reached to a final definition, and thus interpretation of those results or comparisons of prevalence across different studies should be cautious.

In the univariable analysis for the crude sample, the new defined MH was a significantly protective factor for ACM in our nonobese participants. However, after adjustment for potential confounders and PSM, the association changed materially. The mixed results between the original study and the present study might be explained by several reasons. First of all, different BMI categories and cutoffs. In the original study, there were three BMI categories, namely normal weight (BMI, 18.5-24.9 kg/m²), overweight (BMI, 25.0-29.9 kg/m²) and obesity (BMI, ≥ 30 kg/m²). In our study, the participants were all non-obese with BMI less than 28 kg/m². In addition, the cutoff value of WHR may also not be optimal for Chinese people

due to the different ethnicities and baseline characteristics. Secondly, the new MH definition only took SBP into consideration but not DBP since it failed to achieve statistical significance to predict outcomes in the original study. In our study, DBP is also a significant risk factor for ACM. Historical studies have revealed a J-curve relation between DBP and cardiovascular outcomes[29]. as well as cardiovascular and all-cause death[30]. In this case, higher DBP could also potentially lead to adverse prognosis. Thirdly, comparing to traditional metabolic criteria, the biggest distinctions for the new MH definition is the lack of dyslipidemia, which is also a well-established risk factor for CVD and mortality [31, 32].

To our knowledge, this is the first study to assess the role of the new MH definition for ACM in a non-obese Asian population. The negative results based on multiple statistical analyses in the present study indicated that the generalization of the new definition in other populations needs to be validated. This study has several limitations. First, the mortality was relatively low in our study. For the relatively small number of ACM, multivariable models only adjusted for some basic variables to ensure the convergence of the model. On the other hand, for including those covariates, the convergence of the model may be poor, and the results were exploratory. Second, most of the specific cause for death could not be determined. We can only make a conclusion about the relationship between the new MH definition and ACM. Third, the relatively small sample from a single center might also affect the statistical power of the results. Multicenter-based larger studies are needed to confirm and extend the present finding.

Conclusions

In this study, we firstly assessed the performance of the new MH definition, based on SBP, use of BP medication, WHR and self-reported diabetes, for ACM in a non-obese Chinese population. Our results suggested that the risk of total mortality was not significantly different between the non-obese people with MH or MUH classified by this definition. This new MH definition may not be suitable for mortality risk stratification for non-obese Chinese people. Further studies are needed to explore the role of this new MH definition in different populations.

List Of Abbreviations

MH: metabolic health; ACM: all-cause mortality; PS: propensity score; MUH: metabolic unhealthy; MHO: metabolically healthy obesity; NHANES-III: Nutrition Examination Survey; BP: blood pressure; WC: waist circumference; HC: hip circumference; FPG: fasting plasma glucose; TG: triglycerides; TC: total cholesterol; HDL-C :high density lipoprotein-cholesterol; LDL-C: low density lipoprotein cholesterol; CVD: Cardiovascular diseases; SBP: systolic blood pressure; DBP: diastolic blood pressure; WHR: waist to hip ratio; PSM: propensity-score matching; MUNO: metabolically unhealthy non-obese; MONW: metabolically obese normal-weight

Declarations

Acknowledgements

We also would like to thank all the participants and investigators that took part in this study.

Authors' contributions

Study concept and design: Sen He, Ziqiong Wang. Investigating organizer: Muxin Zhang, Haiyan Ruan. Acquisition and cleaning of data: Ye Zhu, Xin Wei, Jiafu Wei. Statistical analysis: Ziqiong Wang, Liying Li. Interpretation of data: Ziqiong Wang. Drafting of the manuscript: Ziqiong Wang, Liying Li. Obtained funding: Xiaoping Chen and Sen He. All authors have read and approved the manuscript.

Funding

This study was supported by a grant from National Key R&D Program of China (Grant No.:2017YFC0910004), National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Grant No.: Z20192010), a project from China's eighth national 5-year research plan (Grant No.: 85-915-01-02) and by megaprojects of science research for China's 11th 5-year plan (Grant No.: 2006BAI01A01)

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The surveys were approved by the Ministry of Health of China, as well as by the Ethics Committee of West China Hospital of Sichuan University. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow diagram

Figure 2

Distribution of propensity scores in the MH and MUH groups. For intervals along the x-axis, the area under the probability density curve represents the probability of those propensity scores, and smoothing was via the kernel density estimate.

Figure 3

Kaplan-Meier (KM) survival curves for all-cause mortality (MH vs. MUH). (A) KM curves in the crude sample; (B) KM curves in the overlap weighting sample; (C) KM curves in the PSM sample.

Supplementary Files

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