Mortality, Cardiovascular and Medication Outcomes in Patients With Myocardial Infarction and Underweight in a Meta-Analysis of 6.3 Million Patients

Chaoxing Lin*[a], MBBS; Wan Hsien Loke*[a], MBBS; Bing Han Ng*[a], MBBS; Yip Han Chin[a], MBBS; Bryan Chong[a], MBBS; Rachel Sze Jen Goh[a], MBBS; Gwyneth Kong[a], MBBS; Christen En Ya Ong[a], MBBS; Kai En Chan[a], MBBS; Clarissa Fu[a], MBBS; Tasha Idnani[a], MBBS; Mark D Muthiah[a,b,c], MBBS; Chin Meng Khoo[a,d], MBBS; Roger Foo[a,e], MD, MBBS; Poay Huan Loh[a,e], MBBCh, BAO; Mark Y Chan[a,e], PhD; Adrian Brown[f,g,h], PhD; Georgios K Dimitriadis[i,j], PhD; Nicholas WS Chew[e], MBChB

[a]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[b]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore

[c]National University Centre for Organ Transplantation, National University Health System, Singapore

[d]Division of Endocrinology, Department of Medicine, National University Hospital, Singapore

[e]Department of Cardiology, National University Heart Centre, National University Health System, Singapore

[f]UCL Centre for Obesity Research, University College London, London, Greater London, United Kingdom

[g]Bariatric Centre for Weight Management and Metabolic Surgery, University College London Hospital NHS Trust, London, Greater London, United Kingdom

[h]National Institute of Health Research, UCLH Biomedical Research Centre, London, Greater London, United Kingdom

[i]Department of Endocrinology ASO/EASO COM, King's College Hospital NHS Foundation Trust, Denmark Hill, London, United Kingdom

[j]Obesity, Type 2 Diabetes and Immunometabolism Research Group, Department of Diabetes, Faculty of Cardiovascular Medicine & Sciences, School of Life Course Sciences, King's College London, London, United Kingdom

*These authors contributed equally to the manuscript as co-first authors.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Correspondence:

Yip Han Chin

Yong Loo Lin School of Medicine, Singapore

10 Medical Dr, Singapore 117597

Tel: +65 8346 3347

Email: yiphan97@gmail.com

ORCID-ID: 0000-0002-8417-5996

Nicholas WS Chew, MBChB, MMED (Singapore), MRCP (UK)

National University Health System, Singapore

5 Lower Kent Ridge Road, Singapore 119074

Tel: +65 6779 5555

Email: nicholas_ws_chew@nuhs.edu.sg

ORCID-ID: 0000-0002-0640-0430

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

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ABSTRACT

Whilst the majority of the current evidence on myocardial infarction focuses on obesity, there is growing evidence that patients who are underweight have unfavorable prognosis. This study aimed to explore the prevalence, clinical characteristics, and prognosis of this at-risk population. Embase and Medline were searched for studies reporting outcomes in populations who were underweight with myocardial infarction. Underweight and normal weight were defined according to the World Health Organization criteria. A single arm meta-analysis of proportions was used to estimate the prevalence of underweight in patients with myocardial infarction, while a meta-analysis of proportions was used to estimate the odds ratio of all-cause mortality, medications prescribed, and cardiovascular outcomes. 21 studies involving 6,368,225 patients were included, of whom 47,866 were underweight. The prevalence of underweight in myocardial infarction patients was 2.96% (95%CI: 1.96% to 4.47%). Despite having fewer classical cardiovascular risk factors, patients who were underweight had 66% higher hazard for mortality (HR:1.66, 95%CI: 1.44 to 1.92, p<0.0001). The mortality of patients who were underweight increased from 14.1% at 30 days to 52.6% at 5 years. Yet, they were less likely to receive guideline-directed medical therapy. Relative to individuals with normal weight, Asian populations who were underweight had higher mortality risks than their Caucasian counterparts (p=0.0062). In conclusion, in patients with myocardial infarction, those who were underweight tend to have poorer prognostic outcomes. A lower body mass index is an independent predictor of mortality, which calls for global efforts in addressing this modifiable risk factor in clinical practice guidelines.

Individuals at the extremes of the weight spectrum, often quantified by body mass index (BMI) >30 kg/m^2 or <18.5 kg/m^2, have been categorized as having unhealthy weight deviations, [1] with increased mortality and reduced quality-adjusted life years in cardiovascular diseases. [2,3,4] Whilst a vast majority of the evidence focus on patients who are overweight or with obesity, [5] there is growing evidence that patients with myocardial infarction (MI) and who are underweight are at increased mortality risk compared to those with normal weight. [6] A low BMI, often associated with cachexia and frailty, is associated with neuroendocrine, metabolic, and inflammatory pathomechanisms. [7,8] The lower adiposity, calorie reserve, and muscle mass may increase host susceptibility to unfavorable prognosis. [9,10] Understanding the prognostic role of having a low body weight in patients with MI can have important implications on the nutritional and weight management strategies of patients [11,12] beyond the traditional pharmacological therapies. [5,13,14,15,16] Whilst previous meta-analyses have highlighted the association between the large spectrum of BMI categories and prognostic outcomes in patients with coronary heart disease, [17-19] this systematic review and meta-analysis will be the first to provide focused analysis on the prevalence, clinical characteristics and prognostic outcomes of patients who were underweight presenting with MI. It also aims to provide insights on the differences in prognosis of individuals who were underweight with MI based on important factors such as race/ethnicity, socioeconomic status and different BMI cut-off values of underweight.

METHODS

This study was registered with PROSPERO (CRD42022319718) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [20] The data that support the findings of this study are available from the corresponding authors upon reasonable request. A search was conducted on Embase and Medline from inception to 16 March 2022 to identify studies relating to the prevalence, epidemiology, and outcomes of MI in populations who were underweight. Keywords relating to “myocardial infarction”, “underweight” and “malnutrition” were searched (Supplementary Methods). References from included meta-analyses were searched for additional articles to be marked for inclusion. References were imported into Endnote 20 for removal of duplicates before screening.

The title and abstract sieve, and full text review were conducted by 3 authors independently (CXL, WHL and BHN). Disputes were resolved by consensus with the involvement of a senior author (NWSC). The inclusion criteria were (1) cohort studies; (2) studies which examined the outcomes of adult (aged 18 and above) participants post-MI; (3) studies which included an underweight BMI group. In our meta-analysis, studies with BMI deviation of up to ±1.5 kg/m^2 away from the World Health Organization (WHO) criterion of underweight were included, where underweight and normal weight were defined as a BMI of < 18.5 kg/m^2 and a BMI between 18.5 and 24.9 kg/m^2 respectively. [1] In the Asia-Pacific region, an individual with a BMI between 18.5 and 22.9 kg/m^2 may be classified as living with normal weight instead. [21] Reviews, meta-analyses, editorials, commentaries, conference abstracts, case-controlled studies, randomized controlled trials and non-English language articles were excluded. Studies examining pediatric populations or those reporting on populations with unique

physiological status including cancer patients were excluded. Studies analyzing results extracted from the same database in overlapping time periods were removed, and the most comprehensive article was retained.

Data was extracted by 3 independent authors (CXL, WHL and BHN) into a structured proforma onto an excel sheet. Data on study characteristics (author, country, region, sample sizes and definitions of the different BMI groups, duration of follow up), patient demographic (baseline characteristics, clinical presentation, medications), and outcomes (long term and in-hospital complications and mortality) were extracted. We extracted the mean and standard deviation for continuous variables, and the number of patients belonging to each category for dichotomous variables. Values extracted were stratified according to populations who were underweight and of normal weight. 30 day, 1 year, 2 years and 5 years survival data was extracted from the articles, and WebPlotDigitizer (Version 4.4) was used to extract data from Kaplan-Meier curves, where possible. In addition, we extracted the unadjusted and adjusted hazard ratios of all-cause mortality (HR) in the articles, noting the potential confounders that were adjusted for. Formulas devised by Wan et al were used to estimate values of mean and standard deviation when they were not provided. [22] The primary outcome was all-cause mortality, defined as death from any cause in the given time period in the patient pool examined, as well as the prevalence of underweight in the MI cohort. The secondary outcomes included cardiac mortality, in-hospital mortality, reinfarction, cerebrovascular accident and cardiogenic shock.

RStudio (Version 4.1.0) was used to conduct 3 types of statistical analysis with the *meta* package. [23] Firstly, for the analysis of baseline characteristics and patient

outcomes reported as dichotomous variables, a single arm meta-analysis was conducted to determine the effect size (ES) using a generalized linear mixed model with Clopper-Pearson intervals using the *metaprop* function. [24,25] The generalized linear mixed model may be better able to account for within-study variation, with the assumption of a binomial likelihood for individual study events. [26] Secondly, to estimate the effect of different BMI categories on dichotomous patient outcomes, a generalized linear mixed model was similarly applied to determine the odds ratios (OR) using the *metabin* function. Thirdly, for the analysis of data reported as continuous variables, a meta-analysis of means was conducted using the inverse variance method with the *metamean* function. Forest and funnel plots were created using the *forest.meta* and *funnel.meta* functions respectively.

Next, Cochrane Review Manager (Version 5.4.1) was used to pool unadjusted and adjusted HR using the inverse variance model according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*. [27] Subgroup analysis was conducted to analyze the difference in outcomes by the definition of low BMI group, geographical region, race/ethnicity, retrospective or prospective studies, single or multi center studies, length of follow-up, type of MI and income group. We followed the World Bank classification of countries for income group according to the gross national income per capita, and geographical region. [28] Individuals descending from East Asia, Central Asia, South Asia and Middle East heritage were defined to be of Asian race/ethnicity.

As the pooled studies differed in trial characteristics such as inclusion and exclusion criteria and study duration, we opted for the recommended approach of

using a random effects model in the analysis. [29] Hartung-Knapp adjustments were utilized to adjust confidence intervals. [23] A p-value of ≤0.05 was considered as statistically significant. Next, I^2 was used to quantify the overall variation across studies that may be attributed to heterogeneity rather than random chance, where an I^2 value of <25%, 25% to 50%, 50% to 75%, and >75% corresponds to minimal, small, moderate, and large amounts of heterogeneity respectively. [29] Publication bias was assessed via a funnel plot.

The Newcastle-Ottawa Scale was used to assess the risk of bias of included articles by 3 independent authors (CXL, WHL and BHN). Disputes were resolved through the consensus of a fourth independent author (YHC). The Newcastle-Ottawa Scale evaluates the bias of cohort studies across 3 domains: (1) the selection of study groups, (2) the comparability of these groups, and (3) the ascertainment of exposure or outcome of interest. [30] The maximum possible score given to a study is 9.

RESULTS

The search yielded 4,390 results, of which 1,124 were duplicates. 2,914 studies were excluded after reviewing the title and abstract, and 352 studies were selected for full text review. In total, 21 studies were selected for this meta-analysis (Supplementary Figure S1). This included 8 articles from East Asia and Pacific, 1 article from Middle East and North Africa, 6 articles from North America, 5 articles from Europe and Central Asia, and 1 article from South Asia. A total of 6,368,225 individuals were included, out of which 47,866 were living with underweight and 5,206,017 were living with normal weight. The mean age of the populations who were underweight and normal weight were 72 and 67 years respectively. The proportion of males in the

populations who were underweight and normal weight were 48.0% and 69.0% respectively, while the mean BMI were 17.3 kg/m^2 and 23.0 kg/m^2 respectively. Of the 47,661 patients who were underweight, 93.0% presented with ST-elevation MI; whilst 97.7% of the 5,204,752 patients with normal weight, presented with ST-elevation MI. The summary of included articles and their risk of bias can be found in Supplementary Table S1. The mean Newcastle-Ottawa Scale score was 7.28, which reflected a high level of quality of evidence.

Among 6,368,225 patients with MI, the overall pooled prevalence rate of patients who were underweight was 2.96% (95%CI: 1.96% to 4.47%, Central Illustration, Table 1). The prevalence of patients who were underweight was significantly higher in populations who were predominantly of Asian race/ethnicity (4.95%, 95%CI: 2.87% to 8.41%) compared to predominantly of Caucasian race/ethnicity (1.84%, 95%CI: 1.10% to 3.05%, p=0.0028). The lower middle-income group had the highest prevalence of patients who were underweight (14.22%, 95%CI: 11.83% to 17.01%), followed by the upper middle-income (3.40%, 95%CI: 2.31% to 5.38%), and the high-income group (2.57%, 95%CI: 1.54% to 4.16%, p<0.0001).

In the comparison of baseline characteristics (Supplementary Table S2), the prevalence of heart failure was significantly higher among patients who were underweight compared to normal weight. However, the prevalence of dyslipidemia, type 2 diabetes mellitus and hypertension were significantly higher among patients with normal weight.

A total of 13 studies (involving 214,382 patients) reported all-cause mortality rates. The temporal trend of all-cause mortality in patients who were underweight and with normal weight is presented in Supplementary Table S3, and a bar plot of the odds ratios can be found in Supplementary Figure S2. In populations who were underweight, the overall pooled mortality rate was 49.12% (95%CI: 28.46% to 70.08%). All-cause mortality rate increased from 14.16% (95%CI: 9.73% to 20.15%) at 30 days to 52.69% (95%CI: 20.65% to 82.65%) at 5 years.

The overall summary for the outcome of all-cause mortality can be seen in Table 2 and Figure 1. There was a significantly increased all-cause mortality risk in patients who were underweight compared to those with normal weight (OR: 2.78, 95%CI: 2.30 to 3.35, p<0.001). Subgroup analysis by race/ethnicity found significantly higher odds of mortality in populations who were predominantly of Asian race/ethnicity (OR: 3.56, 95%CI: 2.74 to 4.62) compared to predominantly of Caucasian race/ethnicity (OR: 2.36, 95%CI: 1.80 to 3.09, p=0.0062). There were no significant differences in all-cause mortality when subgrouped by income group and underweight BMI cut-off. Funnel plot analysis showed no publication bias (Supplementary Figure S3).

Next, a pooled analysis of hazard ratios demonstrated that patients who were underweight had 86% higher hazard for mortality following MI compared to those with normal weight (HR: 1.86, 95%CI: 1.64 to 2.12, p<0.0001). After adjusting for baseline variables such as age, sex, clinical presentation, and interventions, the mortality risk remained significantly higher in the underweight compared to normal weight group (HR: 1.66, 95%CI: 1.44 to 1.92, p<0.0001) (Supplementary Table S4).

Patients who were underweight had increased odds of cardiac mortality (OR: 2.70, 95%CI: 1.86 to 3.92, p=0.0018), in-hospital mortality (OR: 1.91, 95%CI: 1.84 to 1.99, p<0.0001), and cardiogenic shock (OR: 1.11, 95%CI: 1.02 to 1.20, p=0.0364) compared to patients with normal weight (Table 3, Figure 1). However, there were no differences in rates of reinfarction and cerebrovascular accidents between both groups.

Patients who were underweight were less likely to be prescribed glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, beta-blockers, angiotensin receptor blockers or angiotensinogen converting enzyme inhibitors, and statins compared to those with normal weight (Table 3, Figure 1).

DISCUSSION

Whilst the identification of risk factors and targeted management in patients with MI and who are underweight are lacking in current clinical practice guidelines, [31,32] there have been concerning preliminary data from cohort studies demonstrating poor prognosis in these individuals. [5,33] Prior meta-analyses [18,19] have examined the association of the wide range of BMI categories and prognostic outcomes in coronary artery disease, reporting a J-shaped association between mortality and BMI. Our study extends the current knowledge by strengthening this association between underweight and adverse prognosis through findings from a large study population of 6.3 million patients. The advantage of this large meta-analysis allows for comprehensive subgroup analyses based on geographical region, ethnicity, income status, follow-up duration, and MI type, which in turn provides valuable information on the implications for healthcare policy making and clinical practice. Our study highlights that an

estimated 3% of MI patients live with underweight, and 1 in 2 patients who are underweight do not survive beyond 5 years post-MI, despite the lower prevalence of cardiovascular risk factors such as hypertension, dyslipidemia, and type 2 diabetes mellitus compared to other BMI categories. [34,35] Additionally, individuals who are underweight are at higher risks of cardiovascular complications compared to their counterparts who are of normal weight. Notably, patients who are underweight are more likely to be discharged with fewer guideline-directed medical therapy following MI.

The European Society of Cardiology and American Heart Association guidelines recommend lifestyle modifications and the use of prognostically-important medications including antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors, and statins for all patients following MI. [31,32,36] However, our study shows the concerningly lower rates of guideline-directed medical therapy prescribed to patients who were underweight with MI compared to patients who were of normal weight. One plausible explanation might be that they were unsuitable for specific pharmacological therapeutics.[37,38,39] Their frailty and hemodynamic instability may deter the usage of certain drugs such as beta-blockers. [32,40] A more concerning misconception that may explain the lower rates of post-MI medical therapy is the lower rates of classical cardiovascular risk factors associated with these patients. [41,42] The metabolic health of these patients tends to be underestimated since the presence of low BMI may not be entirely benign.[43,44] Low BMI is identified as an independent risk factor for post-MI mortality, which has a reportedly greater predictive value than high BMI. [34,45] In fact, current literature has reported on the presence of an “obesity paradox”, where moderate obesity is associated with a protective effect against

mortality. Recent studies have recognized this issue, with a position paper by the European Association for Predictive, Preventive and Personalized Medicine cautioning against assuming that patients with low borderline “normal” BMI have a desirable body weight. [46] Thus, there is a need to address the misconception that MI patients who are underweight may fare better and require less medical attention. It is important for healthcare professionals to be cognizant that “healthy” patients, based solely on BMI, who are underweight, may in fact have a higher mortality risk than other BMI groups despite having fewer associated cardiovascular comorbidities. There is thus an urgent need for updated clinical practice guidelines on the primary and secondary prevention of MI in patients who are underweight.

Various hypotheses have been proposed to explain the poorer prognostic outcomes in patients who are underweight. [47,48] One of the most plausible hypotheses relates to the lower lean body mass and body fat in these individuals. [49] Lean body mass has beneficial effects on metabolism, while reduced body fat may increase mortality risks due to lowered levels of physiological stores. [50,51,52] However, Bucholz *et. al.*, reported an important observation that increased mortality was evident even in patients without the presence of frailty or significant comorbidities. [5] Moreover, our meta-analysis also alludes to this with underweight being an independent predictor of mortality even after adjusting for important confounders. There may be other unexplored pathophysiological mechanisms underlying the poor prognosis of populations who were underweight that warrant further investigation. Our study suggests potential non-ischemic and non-cardiac pathomechanisms, given that populations who were underweight did not have higher risks of recurrent MI despite being prescribed less statins. [53] Post-MI, these patients may be more susceptible to

certain types of cancer and other frailty-associated diseases. [54] Moreover, the comparatively lower rates of drugs prescribed for patients who were underweight may also contribute to the poor prognosis. Given that underweight is a recently established non-traditional but reversible cardiovascular risk factor, [34,55] a more nuanced understanding behind the pathophysiology and risk factors in these populations will aid in creating targeted and holistic guidelines to improve outcomes post-MI.

The J-shaped association of BMI and morbidity or mortality has been well described in many disease states,[56] with underweight status identified as an adverse prognostic marker. [17,18] Although underweight and undernutrition are often used interchangeably, clinicians need to remain cognizant that underweight is not synonymous to undernutrition. [56,57] Therefore, it is worth investigating whether nutritional measures should be used in tandem with BMI to stratify individuals at higher risks of further complications and mortality. [58,59,60] Although low BMI is an indicator for more aggressive treatment in patients with MI, it may not be the absolute best prognosticating marker for mortality and other outcomes. [61] Nutritional risk tools may be considered instead given their more holistic evaluation of patients.[58,62] Moreover, there is a need to differentiate between patients who have experienced intentional and unintentional weight loss, given that it leads to different outcomes. [63,64] Hence, future studies examining the effectiveness of singular and multiple measures of malnutrition should be conducted to further our understanding of the appropriate tools to use in the context of cardiovascular diseases. [65]

We highlight that the mortality burden associated with underweight is a global health issue that does not discriminate between populations based on socio-economic

status. Even though the prevalence of those who were underweight and with MI was greater in the lower middle-income countries, partly due to the higher absolute prevalence of individuals who were underweight in these countries, [66,67] mortality rates between the various income groups were similar. This calls for concerted multinational efforts in addressing underweight and malnutrition globally, including countries with traditionally lower rates. Moreover, individuals of Asian race/ethnicity appeared to have lower BMI and at higher risk of death after MI than individuals of Caucasian race/ethnicity, indicating that adequate nutrition is important in preserving health during illness as well. Individuals from Asian heritage tend to have lower levels of lean body mass but are at higher risks of developing type 2 diabetes mellitus, [68] predisposing to advanced coronary artery disease. [50,51,69,70] The higher levels of cholesterol in traditional Asian cuisine, [11,71] and increased rates of smoking and alcohol consumption amongst those of Asian race/ethnicity are known drivers for cardiovascular diseases. [72-75] Given the interplay of genetic and lifestyle factors,[76] poorer prognostic outcomes in patient of Asian race/ethnicity may still be observed at higher BMI ranges above the underweight BMI cut-off. Future studies should consider examining the relevance of race/ethnicity in the categorization of cardiovascular disease risk by BMI groups.

However, the study has its limitations. Most studies originated from the high-income countries, decreasing the generalizability of our findings. Additionally, there was a lack of mortality data from the lower middle-income countries, and a paucity of data from the geographical regions of Middle East & North Africa, and South Asia. Despite these limitations, the data allow our readers a glimpse into the potential differences in underweight MI in different countries. Future studies should examine if

these findings are applicable to other parts of the world. Next, given that the individual's BMI may change over time, the baseline BMI data used to categorize individuals may not be fully representative of the BMI trends and survival over time. [77] Lastly, patients who were underweight in our meta-analysis tended to be older with more comorbidities, resulting in poorer outcomes such as higher mortality rates. [78] Thus, the results may be less applicable to younger patients who are underweight and with fewer comorbidities. Moreover, there was a significantly lower proportion of males in the underweight population. However, we were unable to conduct more detailed analysis with stratification by age and sex due to the paucity of data in the included studies. Nonetheless, the significantly higher adjusted hazard ratio of all-cause mortality in the underweight population compared to the normal weight population illustrates the general differences in prognostic outcomes between the 2 groups of patients.

In conclusion, up to 3% of all MI patients are living with underweight and they tend to have poorer prognostic outcomes compared to patients with normal weight. Lower middle-income and Asian-predominant populations are also at higher risk of being underweight and having poorer prognosis respectively. Ultimately, there is a need for adequate nutrition and aggressive treatment despite the lack of classical cardiovascular risk factors in these overlooked patients. This calls for concerted efforts in addressing this non-traditional but modifiable risk factor in clinical practice for patients who are underweight. Further studies are necessary to shed light on the pathophysiology between underweight and higher mortality rates in patients with MI.

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Author contributions

Conceptualization – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Nicholas WS Chew

Data curation – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Christen En Ya Ong, Kai En Chan, Clarissa Fu, Tasha Idnani, Rachel Sze Jen Goh

Formal analysis – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Christen En Ya Ong, Kai En Chan, Clarissa Fu, Tasha Idnani, Rachel Sze Jen Goh

Supervision –Mark D. Muthiah, Chin Meng Khoo, Roger Foo, Poay Huan Loh, Mark Y Chan, Adrian Brown, Georgios K Dimitriadis, Nicholas WS Chew

Validation – Yip Han Chin, Tasha Idnani, Rachel Sze Jen Goh, Mark D. Muthiah, Chin Meng Khoo, Roger Foo, Poay Huan Loh, Mark Y Chan, Adrian Brown, Georgios K Dimitriadis, Nicholas WS Chew

Writing, original draft – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Nicholas WS Chew

Writing, review, and editing – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Christen En Ya Ong, Kai En Chan, Clarissa Fu, Tasha Idnani, Rachel Sze Jen Goh, Mark D. Muthiah, Chin Meng Khoo, Roger Foo, Poay Huan Loh, Mark Y Chan, Adrian Brown, Georgios K Dimitriadis, Nicholas WS Chew

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FIGURE TITLES AND LEGENDS

Central Illustration: Prevalence of and outcomes in patients who were underweight with myocardial infarction

Figure 1: Summary plot of outcomes and medications in patients who were underweight compared to normal weight

SUPPLEMENTARY MATERIAL

Supplementary Methods. Search strategy for Medline

Supplementary Table S1. Summary of included articles

Supplementary Table S2. Pooled baseline characteristics of included articles, stratified by populations who were underweight and of normal weight

Supplementary Table S3. All-cause mortality following myocardial infarction, stratified by follow-up duration

Supplementary Table S4. Hazard ratio of all-cause mortality following myocardial infarction in populations who were underweight compared to normal weight

Supplementary Figure S1. PRISMA flow diagram

Supplementary Figure S2. Bar plot of the temporal trend of all-cause mortality outcome in patients who were underweight and of normal weight

Supplementary Figure S3. Funnel plot of all-cause mortality outcome in patients who were underweight and of normal weight

Mortality, Cardiovascular and Medication Outcomes in Patients With Myocardial Infarction and Underweight in a Meta-Analysis of 6.3 Million Patients

Chaoxing Lin*[a], MBBS; Wan Hsien Loke*[a], MBBS; Bing Han Ng*[a], MBBS; Yip Han Chin[a], MBBS; Bryan Chong[a], MBBS; Rachel Sze Jen Goh[a], MBBS; Gwyneth Kong[a], MBBS; Christen En Ya Ong[a], MBBS; Kai En Chan[a], MBBS; Clarissa Fu[a], MBBS; Tasha Idnani[a], MBBS; Mark D Muthiah[a,b,c], MBBS; Chin Meng Khoo[a,d], MBBS; Roger Foo[a,e], MD, MBBS; Poay Huan Loh[a,e], MBBCh, BAO; Mark Y Chan[a,e], PhD; Adrian Brown[f,g,h], PhD; Georgios K Dimitriadis[i,j], PhD; Nicholas WS Chew[e], MBChB

[a]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[b]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore

[c]National University Centre for Organ Transplantation, National University Health System, Singapore

[d]Division of Endocrinology, Department of Medicine, National University Hospital, Singapore

[e]Department of Cardiology, National University Heart Centre, National University Health System, Singapore

[f]UCL Centre for Obesity Research, University College London, London, Greater London, United Kingdom

[g]Bariatric Centre for Weight Management and Metabolic Surgery, University College London Hospital NHS Trust, London, Greater London, United Kingdom

[h]National Institute of Health Research, UCLH Biomedical Research Centre, London, Greater London, United Kingdom

[i]Department of Endocrinology ASO/EASO COM, King's College Hospital NHS Foundation Trust, Denmark Hill, London, United Kingdom

[j]Obesity, Type 2 Diabetes and Immunometabolism Research Group, Department of Diabetes, Faculty of Cardiovascular Medicine & Sciences, School of Life Course Sciences, King's College London, London, United Kingdom

*These authors contributed equally to the manuscript as co-first authors.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Running title: Outcomes in underweight patients with MI

Correspondence:

Yip Han Chin

Yong Loo Lin School of Medicine, Singapore

10 Medical Dr, Singapore 117597

Tel: +65 8346 3347

Email: yiphan97@gmail.com

ORCID-ID: 0000-0002-8417-5996

Nicholas WS Chew, MBChB, MMED (Singapore), MRCP (UK)

National University Health System, Singapore

5 Lower Kent Ridge Road, Singapore 119074

Tel: +65 6779 5555

Email: nicholas_ws_chew@nuhs.edu.sg

ORCID-ID: 0000-0002-0640-0430

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Keywords: Myocardial Infarction, Underweight, Body Mass Index, Meta-Analysis and Systematic Review

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ABSTRACT

Whilst the majority of the current evidence on myocardial infarction focuses on obesity, there is growing evidence that patients who are underweight have unfavorable prognosis. This study aimed to explore the prevalence, clinical characteristics, and prognosis of this at-risk population. Embase and Medline were searched for studies reporting outcomes in populations who were underweight with myocardial infarction. Underweight and normal weight were defined according to the World Health Organization criteria. A single arm meta-analysis of proportions was used to estimate the prevalence of underweight in patients with myocardial infarction, while a meta-analysis of proportions was used to estimate the odds ratio of all-cause mortality, medications prescribed, and cardiovascular outcomes. 21 studies involving 6,368,225 patients were included, of whom 47,866 were underweight. The prevalence of underweight in myocardial infarction patients was 2.96% (95%CI: 1.96% to 4.47%). Despite having fewer classical cardiovascular risk factors, patients who were underweight had 66% higher hazard for mortality (HR:1.66, 95%CI: 1.44 to 1.92, p<0.0001). The mortality of patients who were underweight increased from 14.1% at 30 days to 52.6% at 5 years. Yet, they were less likely to receive guideline-directed medical therapy. Relative to individuals with normal weight, Asian populations who were underweight had higher mortality risks than their Caucasian counterparts (p=0.0062). In conclusion, in patients with myocardial infarction, those who were underweight tend to have poorer prognostic outcomes. A lower body mass index is an independent predictor of mortality, which calls for global efforts in addressing this modifiable risk factor in clinical practice guidelines.

Individuals at the extremes of the weight spectrum, often quantified by body mass index (BMI) >30 kg/m^2 or <18.5 kg/m^2, have been categorized as having unhealthy weight deviations, [1] with increased mortality and reduced quality-adjusted life years in cardiovascular diseases. [2,3,4] Whilst a vast majority of the evidence focus on patients who are overweight or with obesity, [5] there is growing evidence that patients with myocardial infarction (MI) and who are underweight are at increased mortality risk compared to those with normal weight. [6] A low BMI, often associated with cachexia and frailty, is associated with neuroendocrine, metabolic, and inflammatory pathomechanisms. [7,8] The lower adiposity, calorie reserve, and muscle mass may increase host susceptibility to unfavorable prognosis. [9,10] Understanding the prognostic role of having a low body weight in patients with MI can have important implications on the nutritional and weight management strategies of patients [11,12] beyond the traditional pharmacological therapies. [5,13,14,15,16] Whilst previous meta-analyses have highlighted the association between the large spectrum of BMI categories and prognostic outcomes in patients with coronary heart disease, [17-19] this systematic review and meta-analysis will be the first to provide focused analysis on the prevalence, clinical characteristics and prognostic outcomes of patients who were underweight presenting with MI. It also aims to provide insights on the differences in prognosis of individuals who were underweight with MI based on important factors such as race/ethnicity, socioeconomic status and different BMI cut-off values of underweight.

METHODS

This study was registered with PROSPERO (CRD42022319718) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [20] The data that support the findings of this study are available from the corresponding authors upon reasonable request. A search was conducted on Embase and Medline from inception to 16 March 2022 to identify studies relating to the prevalence, epidemiology, and outcomes of MI in populations who were underweight. Keywords relating to “myocardial infarction”, “underweight” and “malnutrition” were searched (Supplementary Methods). References from included meta-analyses were searched for additional articles to be marked for inclusion. References were imported into Endnote 20 for removal of duplicates before screening.

The title and abstract sieve, and full text review were conducted by 3 authors independently (CXL, WHL and BHN). Disputes were resolved by consensus with the involvement of a senior author (NWSC). The inclusion criteria were (1) cohort studies; (2) studies which examined the outcomes of adult (aged 18 and above) participants post-MI; (3) studies which included an underweight BMI group. In our meta-analysis, studies with BMI deviation of up to ±1.5 kg/m^2 away from the World Health Organization (WHO) criterion of underweight were included, where underweight and normal weight were defined as a BMI of < 18.5 kg/m^2 and a BMI between 18.5 and 24.9 kg/m^2 respectively. [1] In the Asia-Pacific region, an individual with a BMI between 18.5 and 22.9 kg/m^2 may be classified as living with normal weight instead. [21] Reviews, meta-analyses, editorials, commentaries, conference abstracts, case-controlled studies, randomized controlled trials and non-English language articles were excluded. Studies examining pediatric populations or those reporting on populations with unique

physiological status including cancer patients were excluded. Studies analyzing results extracted from the same database in overlapping time periods were removed, and the most comprehensive article was retained.

Data was extracted by 3 independent authors (CXL, WHL and BHN) into a structured proforma onto an excel sheet. Data on study characteristics (author, country, region, sample sizes and definitions of the different BMI groups, duration of follow up), patient demographic (baseline characteristics, clinical presentation, medications), and outcomes (long term and in-hospital complications and mortality) were extracted. We extracted the mean and standard deviation for continuous variables, and the number of patients belonging to each category for dichotomous variables. Values extracted were stratified according to populations who were underweight and of normal weight. 30 day, 1 year, 2 years and 5 years survival data was extracted from the articles, and WebPlotDigitizer (Version 4.4) was used to extract data from Kaplan-Meier curves, where possible. In addition, we extracted the unadjusted and adjusted hazard ratios of all-cause mortality (HR) in the articles, noting the potential confounders that were adjusted for. Formulas devised by Wan et al were used to estimate values of mean and standard deviation when they were not provided. [22] The primary outcome was all-cause mortality, defined as death from any cause in the given time period in the patient pool examined, as well as the prevalence of underweight in the MI cohort. The secondary outcomes included cardiac mortality, in-hospital mortality, reinfarction, cerebrovascular accident and cardiogenic shock.

RStudio (Version 4.1.0) was used to conduct 3 types of statistical analysis with the *meta* package. [23] Firstly, for the analysis of baseline characteristics and patient

outcomes reported as dichotomous variables, a single arm meta-analysis was conducted to determine the effect size (ES) using a generalized linear mixed model with Clopper-Pearson intervals using the *metaprop* function. [24,25] The generalized linear mixed model may be better able to account for within-study variation, with the assumption of a binomial likelihood for individual study events. [26] Secondly, to estimate the effect of different BMI categories on dichotomous patient outcomes, a generalized linear mixed model was similarly applied to determine the odds ratios (OR) using the *metabin* function. Thirdly, for the analysis of data reported as continuous variables, a meta-analysis of means was conducted using the inverse variance method with the *metamean* function. Forest and funnel plots were created using the *forest.meta* and *funnel.meta* functions respectively.

Next, Cochrane Review Manager (Version 5.4.1) was used to pool unadjusted and adjusted HR using the inverse variance model according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*. [27] Subgroup analysis was conducted to analyze the difference in outcomes by the definition of low BMI group, geographical region, race/ethnicity, retrospective or prospective studies, single or multi center studies, length of follow-up, type of MI and income group. We followed the World Bank classification of countries for income group according to the gross national income per capita, and geographical region. [28] Individuals descending from East Asia, Central Asia, South Asia and Middle East heritage were defined to be of Asian race/ethnicity.

As the pooled studies differed in trial characteristics such as inclusion and exclusion criteria and study duration, we opted for the recommended approach of

using a random effects model in the analysis. [29] Hartung-Knapp adjustments were utilized to adjust confidence intervals. [23] A p-value of ≤0.05 was considered as statistically significant. Next, I^2 was used to quantify the overall variation across studies that may be attributed to heterogeneity rather than random chance, where an I^2 value of <25%, 25% to 50%, 50% to 75%, and >75% corresponds to minimal, small, moderate, and large amounts of heterogeneity respectively. [29] Publication bias was assessed via a funnel plot.

The Newcastle-Ottawa Scale was used to assess the risk of bias of included articles by 3 independent authors (CXL, WHL and BHN). Disputes were resolved through the consensus of a fourth independent author (YHC). The Newcastle-Ottawa Scale evaluates the bias of cohort studies across 3 domains: (1) the selection of study groups, (2) the comparability of these groups, and (3) the ascertainment of exposure or outcome of interest. [30] The maximum possible score given to a study is 9.

RESULTS

The search yielded 4,390 results, of which 1,124 were duplicates. 2,914 studies were excluded after reviewing the title and abstract, and 352 studies were selected for full text review. In total, 21 studies were selected for this meta-analysis (Supplementary Figure S1). This included 8 articles from East Asia and Pacific, 1 article from Middle East and North Africa, 6 articles from North America, 5 articles from Europe and Central Asia, and 1 article from South Asia. A total of 6,368,225 individuals were included, out of which 47,866 were living with underweight and 5,206,017 were living with normal weight. The mean age of the populations who were underweight and normal weight were 72 and 67 years respectively. The proportion of males in the

populations who were underweight and normal weight were 48.0% and 69.0% respectively, while the mean BMI were 17.3 kg/m^2 and 23.0 kg/m^2 respectively. Of the 47,661 patients who were underweight, 93.0% presented with ST-elevation MI; whilst 97.7% of the 5,204,752 patients with normal weight, presented with ST-elevation MI. The summary of included articles and their risk of bias can be found in Supplementary Table S1. The mean Newcastle-Ottawa Scale score was 7.28, which reflected a high level of quality of evidence.

Among 6,368,225 patients with MI, the overall pooled prevalence rate of patients who were underweight was 2.96% (95%CI: 1.96% to 4.47%, Central Illustration, Table 1). The prevalence of patients who were underweight was significantly higher in populations who were predominantly of Asian race/ethnicity (4.95%, 95%CI: 2.87% to 8.41%) compared to predominantly of Caucasian race/ethnicity (1.84%, 95%CI: 1.10% to 3.05%, p=0.0028). The lower middle-income group had the highest prevalence of patients who were underweight (14.22%, 95%CI: 11.83% to 17.01%), followed by the upper middle-income (3.40%, 95%CI: 2.31% to 5.38%), and the high-income group (2.57%, 95%CI: 1.54% to 4.16%, p<0.0001).

In the comparison of baseline characteristics (Supplementary Table S2), the prevalence of heart failure was significantly higher among patients who were underweight compared to normal weight. However, the prevalence of dyslipidemia, type 2 diabetes mellitus and hypertension were significantly higher among patients with normal weight.

A total of 13 studies (involving 214,382 patients) reported all-cause mortality rates. The temporal trend of all-cause mortality in patients who were underweight and with normal weight is presented in Supplementary Table S3, and a bar plot of the odds ratios can be found in Supplementary Figure S2. In populations who were underweight, the overall pooled mortality rate was 49.12% (95%CI: 28.46% to 70.08%). All-cause mortality rate increased from 14.16% (95%CI: 9.73% to 20.15%) at 30 days to 52.69% (95%CI: 20.65% to 82.65%) at 5 years.

The overall summary for the outcome of all-cause mortality can be seen in Table 2 and Figure 1. There was a significantly increased all-cause mortality risk in patients who were underweight compared to those with normal weight (OR: 2.78, 95%CI: 2.30 to 3.35, p<0.001). Subgroup analysis by race/ethnicity found significantly higher odds of mortality in populations who were predominantly of Asian race/ethnicity (OR: 3.56, 95%CI: 2.74 to 4.62) compared to predominantly of Caucasian race/ethnicity (OR: 2.36, 95%CI: 1.80 to 3.09, p=0.0062). There were no significant differences in all-cause mortality when subgrouped by income group and underweight BMI cut-off. Funnel plot analysis showed no publication bias (Supplementary Figure S3).

Next, a pooled analysis of hazard ratios demonstrated that patients who were underweight had 86% higher hazard for mortality following MI compared to those with normal weight (HR: 1.86, 95%CI: 1.64 to 2.12, p<0.0001). After adjusting for baseline variables such as age, sex, clinical presentation, and interventions, the mortality risk remained significantly higher in the underweight compared to normal weight group (HR: 1.66, 95%CI: 1.44 to 1.92, p<0.0001) (Supplementary Table S4).

Patients who were underweight had increased odds of cardiac mortality (OR: 2.70, 95%CI: 1.86 to 3.92, p=0.0018), in-hospital mortality (OR: 1.91, 95%CI: 1.84 to 1.99, p<0.0001), and cardiogenic shock (OR: 1.11, 95%CI: 1.02 to 1.20, p=0.0364) compared to patients with normal weight (Table 3, Figure 1). However, there were no differences in rates of reinfarction and cerebrovascular accidents between both groups.

Patients who were underweight were less likely to be prescribed glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, beta-blockers, angiotensin receptor blockers or angiotensinogen converting enzyme inhibitors, and statins compared to those with normal weight (Table 3, Figure 1).

DISCUSSION

Whilst the identification of risk factors and targeted management in patients with MI and who are underweight are lacking in current clinical practice guidelines, [31,32] there have been concerning preliminary data from cohort studies demonstrating poor prognosis in these individuals. [5,33] Prior meta-analyses [18,19] have examined the association of the wide range of BMI categories and prognostic outcomes in coronary artery disease, reporting a J-shaped association between mortality and BMI. Our study extends the current knowledge by strengthening this association between underweight and adverse prognosis through findings from a large study population of 6.3 million patients. The advantage of this large meta-analysis allows for comprehensive subgroup analyses based on geographical region, ethnicity, income status, follow-up duration, and MI type, which in turn provides valuable information on the implications for healthcare policy making and clinical practice. Our study highlights that an

estimated 3% of MI patients live with underweight, and 1 in 2 patients who are underweight do not survive beyond 5 years post-MI, despite the lower prevalence of cardiovascular risk factors such as hypertension, dyslipidemia, and type 2 diabetes mellitus compared to other BMI categories. [34,35] Additionally, individuals who are underweight are at higher risks of cardiovascular complications compared to their counterparts who are of normal weight. Notably, patients who are underweight are more likely to be discharged with fewer guideline-directed medical therapy following MI.

The European Society of Cardiology and American Heart Association guidelines recommend lifestyle modifications and the use of prognostically-important medications including antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors, and statins for all patients following MI. [31,32,36] However, our study shows the concerningly lower rates of guideline-directed medical therapy prescribed to patients who were underweight with MI compared to patients who were of normal weight. One plausible explanation might be that they were unsuitable for specific pharmacological therapeutics.[37,38,39] Their frailty and hemodynamic instability may deter the usage of certain drugs such as beta-blockers. [32,40] A more concerning misconception that may explain the lower rates of post-MI medical therapy is the lower rates of classical cardiovascular risk factors associated with these patients. [41,42] The metabolic health of these patients tends to be underestimated since the presence of low BMI may not be entirely benign.[43,44] Low BMI is identified as an independent risk factor for post-MI mortality, which has a reportedly greater predictive value than high BMI. [34,45] In fact, current literature has reported on the presence of an “obesity paradox”, where moderate obesity is associated with a protective effect against

mortality. Recent studies have recognized this issue, with a position paper by the European Association for Predictive, Preventive and Personalized Medicine cautioning against assuming that patients with low borderline “normal” BMI have a desirable body weight. [46] Thus, there is a need to address the misconception that MI patients who are underweight may fare better and require less medical attention. It is important for healthcare professionals to be cognizant that “healthy” patients, based solely on BMI, who are underweight, may in fact have a higher mortality risk than other BMI groups despite having fewer associated cardiovascular comorbidities. There is thus an urgent need for updated clinical practice guidelines on the primary and secondary prevention of MI in patients who are underweight.

Various hypotheses have been proposed to explain the poorer prognostic outcomes in patients who are underweight. [47,48] One of the most plausible hypotheses relates to the lower lean body mass and body fat in these individuals. [49] Lean body mass has beneficial effects on metabolism, while reduced body fat may increase mortality risks due to lowered levels of physiological stores. [50,51,52] However, Bucholz *et. al.*, reported an important observation that increased mortality was evident even in patients without the presence of frailty or significant comorbidities. [5] Moreover, our meta-analysis also alludes to this with underweight being an independent predictor of mortality even after adjusting for important confounders. There may be other unexplored pathophysiological mechanisms underlying the poor prognosis of populations who were underweight that warrant further investigation. Our study suggests potential non-ischemic and non-cardiac pathomechanisms, given that populations who were underweight did not have higher risks of recurrent MI despite being prescribed less statins. [53] Post-MI, these patients may be more susceptible to

certain types of cancer and other frailty-associated diseases. [54] Moreover, the comparatively lower rates of drugs prescribed for patients who were underweight may also contribute to the poor prognosis. Given that underweight is a recently established non-traditional but reversible cardiovascular risk factor, [34,55] a more nuanced understanding behind the pathophysiology and risk factors in these populations will aid in creating targeted and holistic guidelines to improve outcomes post-MI.

The J-shaped association of BMI and morbidity or mortality has been well described in many disease states,[56] with underweight status identified as an adverse prognostic marker. [17,18] Although underweight and undernutrition are often used interchangeably, clinicians need to remain cognizant that underweight is not synonymous to undernutrition. [56,57] Therefore, it is worth investigating whether nutritional measures should be used in tandem with BMI to stratify individuals at higher risks of further complications and mortality. [58,59,60] Although low BMI is an indicator for more aggressive treatment in patients with MI, it may not be the absolute best prognosticating marker for mortality and other outcomes. [61] Nutritional risk tools may be considered instead given their more holistic evaluation of patients.[58,62] Moreover, there is a need to differentiate between patients who have experienced intentional and unintentional weight loss, given that it leads to different outcomes. [63,64] Hence, future studies examining the effectiveness of singular and multiple measures of malnutrition should be conducted to further our understanding of the appropriate tools to use in the context of cardiovascular diseases. [65]

We highlight that the mortality burden associated with underweight is a global health issue that does not discriminate between populations based on socio-economic

status. Even though the prevalence of those who were underweight and with MI was greater in the lower middle-income countries, partly due to the higher absolute prevalence of individuals who were underweight in these countries, [66,67] mortality rates between the various income groups were similar. This calls for concerted multinational efforts in addressing underweight and malnutrition globally, including countries with traditionally lower rates. Moreover, individuals of Asian race/ethnicity appeared to have lower BMI and at higher risk of death after MI than individuals of Caucasian race/ethnicity, indicating that adequate nutrition is important in preserving health during illness as well. Individuals from Asian heritage tend to have lower levels of lean body mass but are at higher risks of developing type 2 diabetes mellitus, [68] predisposing to advanced coronary artery disease. [50,51,69,70] The higher levels of cholesterol in traditional Asian cuisine, [11,71] and increased rates of smoking and alcohol consumption amongst those of Asian race/ethnicity are known drivers for cardiovascular diseases. [72-75] Given the interplay of genetic and lifestyle factors,[76] poorer prognostic outcomes in patient of Asian race/ethnicity may still be observed at higher BMI ranges above the underweight BMI cut-off. Future studies should consider examining the relevance of race/ethnicity in the categorization of cardiovascular disease risk by BMI groups.

However, the study has its limitations. Most studies originated from the high-income countries, decreasing the generalizability of our findings. Additionally, there was a lack of mortality data from the lower middle-income countries, and a paucity of data from the geographical regions of Middle East & North Africa, and South Asia. Despite these limitations, the data allow our readers a glimpse into the potential differences in underweight MI in different countries. Future studies should examine if

these findings are applicable to other parts of the world. Next, given that the individual's BMI may change over time, the baseline BMI data used to categorize individuals may not be fully representative of the BMI trends and survival over time. [77] Lastly, patients who were underweight in our meta-analysis tended to be older with more comorbidities, resulting in poorer outcomes such as higher mortality rates. [78] Thus, the results may be less applicable to younger patients who are underweight and with fewer comorbidities. Moreover, there was a significantly lower proportion of males in the underweight population. However, we were unable to conduct more detailed analysis with stratification by age and sex due to the paucity of data in the included studies. Nonetheless, the significantly higher adjusted hazard ratio of all-cause mortality in the underweight population compared to the normal weight population illustrates the general differences in prognostic outcomes between the 2 groups of patients.

In conclusion, up to 3% of all MI patients are living with underweight and they tend to have poorer prognostic outcomes compared to patients with normal weight. Lower middle-income and Asian-predominant populations are also at higher risk of being underweight and having poorer prognosis respectively. Ultimately, there is a need for adequate nutrition and aggressive treatment despite the lack of classical cardiovascular risk factors in these overlooked patients. This calls for concerted efforts in addressing this non-traditional but modifiable risk factor in clinical practice for patients who are underweight. Further studies are necessary to shed light on the pathophysiology between underweight and higher mortality rates in patients with MI.

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Author contributions

Conceptualization – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Nicholas WS Chew

Data curation – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Christen En Ya Ong, Kai En Chan, Clarissa Fu, Tasha Idnani, Rachel Sze Jen Goh

Formal analysis – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Christen En Ya Ong, Kai En Chan, Clarissa Fu, Tasha Idnani, Rachel Sze Jen Goh

Supervision –Mark D. Muthiah, Chin Meng Khoo, Roger Foo, Poay Huan Loh, Mark Y Chan, Adrian Brown, Georgios K Dimitriadis, Nicholas WS Chew

Validation – Yip Han Chin, Tasha Idnani, Rachel Sze Jen Goh, Mark D. Muthiah, Chin Meng Khoo, Roger Foo, Poay Huan Loh, Mark Y Chan, Adrian Brown, Georgios K Dimitriadis, Nicholas WS Chew

Writing, original draft – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Nicholas WS Chew

Writing, review, and editing – Chaoxing Lin, Wan Hsien Loke, Bing Han Ng, Yip Han Chin, Gwyneth Kong, Bryan Chong, Christen En Ya Ong, Kai En Chan, Clarissa Fu, Tasha Idnani, Rachel Sze Jen Goh, Mark D. Muthiah, Chin Meng Khoo, Roger Foo, Poay Huan Loh, Mark Y Chan, Adrian Brown, Georgios K Dimitriadis, Nicholas WS Chew

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FIGURE TITLES AND LEGENDS

Central Illustration: Prevalence of and outcomes in patients who were underweight with myocardial infarction

Figure 1: Summary plot of outcomes and medications in patients who were underweight compared to normal weight

SUPPLEMENTARY MATERIAL

Supplementary Methods. Search strategy for Medline

Supplementary Table S1. Summary of included articles

Supplementary Table S2. Pooled baseline characteristics of included articles, stratified by populations who were underweight and of normal weight

Supplementary Table S3. All-cause mortality following myocardial infarction, stratified by follow-up duration

Supplementary Table S4. Hazard ratio of all-cause mortality following myocardial infarction in populations who were underweight compared to normal weight

Supplementary Figure S1. PRISMA flow diagram

Supplementary Figure S2. Bar plot of the temporal trend of all-cause mortality outcome in patients who were underweight and of normal weight

Supplementary Figure S3. Funnel plot of all-cause mortality outcome in patients who were underweight and of normal weight

Table 1. Prevalence of individuals who were underweight in the myocardial infarction cohort

	Studies	ES (95% CI)	I^2	p-value
Overall	21	2.96% (1.96 to 4.47%)	99.9	-
Race/Ethnicity[a]				**0.0028**
Predominantly Asian	10	4.95% (2.87 to 8.41%)	99.2%	
Predominantly Caucasian	11	1.84% (1.10 to 3.05%)	100.0%	
Income group				**9×10^{-22}**
High	16	2.57% (1.54 to 4.16%)	99.9	
Upper middle	4	3.40% (2.13 to 5.38%)	87.6	
Lower middle	1	14.22% (11.83 to 17.01%)	-	
Region				**3×10^{-37}**
East Asia & Pacific	8	5.11% (3.14 to 8.21%)	99.2%	
Middle East & North Africa	1	1.21% (0.82 to 1.76%)	-	
North America	6	2.09% (1.01 to 4.28%)	100.0%	
Europe & Central Asia	5	1.57% (0.57 to 4.21%)	96.0%	
South Asia	1	14.22% (11.83 to 17.01%)	-	

Retrospective/ Prospective				0.3627
Retrospective	9	2.41% (1.17 to 4.90%)	99.9%	
Prospective	12	3.46% (1.99 to 5.94%)	99.1%	
Single/ Multi Center				0.7239
Multi center	13	2.81% (1.61 to 4.85%)	100.0%	
Single center	8	3.24% (1.52 to 6.78%)	98.1%	
Type of MI				0.4344
Any	15	3.26% (1.97 to 5.35%)	99.9%	
STEMI	5	2.14% (0.66 to 6.74%)	99.6%	
NSTEMI	1	3.59% (3.40 to 3.79%)	-	

MI – Myocardial infarction, ES – Effect size, CI – Confidence interval, STEMI – ST-elevation MI, NSTEMI – Non ST-elevation MI
[a]Predominantly Asian included all Asian race/ethnicity
Bolded values indicate p-value of <0.05 and it is taken as statistical significance.

Table 2. All-cause mortality outcomes following myocardial infarction, pooled and stratified by subgroups

		Underweight			Normal weight			Comparison of underweight against normal weight		
	Studies	**ES (95% CI)**	**I^2**	**p-value**	**ES (95% CI)**	**I^2**	**p-value**	**OR (95% CI)**	**I^2**	**p-value**
Overall	13	49.12% (28.46 to 70.08%)	99.3%		26.01% (12.82 to 45.66%)	100.0%		2.78 (2.30 to 3.35)	77.4%	**6×10^{-8}**
Race/Ethnicity[a]				0.1207			**0.0220**			**0.0062**
Predominantly Asian	6	34.49% (21.70 to 50.00%)	87.1%		13.67% (8.25 to 21.82%)	96.7%		3.56 (2.74 to 4.62)	26.1%	
Predominantly Caucasian	7	61.34% (23.74 to 88.99%)	99.5%		41.06% (13.60 to 75.51%)	100.0%		2.36 (1.80 to 3.09)	80.6%	
Region[b]				0.0768			**0.0113**			**0.0317**
East Asia & Pacific	5	31.74% (18.72 to 48.42%)	87.9%		12.46% (6.86 to 21.56%)	96.9%		3.51 (2.62 to 4.71)	39.0%	
Middle East & North Africa	1	53.85% (35.05 to 71.61%)	-		21.36% (18.31 to 24.77%)	-		4.30 (1.94 to 9.51)	-	
North America	4	76.44% (13.62 to 98.52%)	99.7%		57.72% (10.18 to 94.27%)	100.0%		2.41 (1.44 to 4.04)	89.4%	
Europe & Central Asia	3	37.52% (6.47 to 83.91%)	93.0%		22.14% (1.54 to 83.78%)	99.9%		2.26 (1.26 to 4.08)	26.0%	

Definition of underweight				**0.0046**			0.1350			0.7415
<18.5 kg/m^2	10	57.11% (30.81 to 79.92%)	99.3%		32.07% (13.81 to 58.19%)	100.0%		2.82 (2.26 to 3.52)	81.2%	
<20.0 kg/m^2	3	24.42% (15.84 to 35.67%)	0.0%		11.59% (5.20 to 23.85%)	92.0%		2.63 (1.16 to 5.94)	60.1%	
Retrospective/ Prospective				0.1862			0.1552			0.7982
Retrospective	3	62.77% (33.84 to 84.75%)	62.2%		42.74% (8.02 to 86.48%)	99.6%		2.95 (1.21 to 7.17)	75.2%	
Prospective	10	44.16% (20.29 to 71.07%)	99.4%		21.89% (8.73 to 45.09%)	100.0%		2.78 (2.24 to 3.45)	79.8%	
Income group[c]				0.2840			0.1751			0.8381
High	11	51.64% (27.16 to 73.56%)	99.4%		27.77% (11.95 to 52.13%)	100.0%		2.75 (2.24 to 3.38)	78.3%	
Upper middle	2	37.83% (3.20 to 91.81%)	68.8%		16.88% (8.77 to 30.03%)	61.0%		2.91 (0.10 to 86.37)	80.0%	
Single/ Multi Centre				0.6663			0.5866			0.2801

Single center	6	44.80% (30.62 to 59.89%)	74.6%		22.01% (11.01 to 39.18%)	99.4%		3.17 (2.31 to 4.35)	63.6%	
Multi center	7	52.86% (16.45 to 86.46%)	99.6%		29.83% (7.43 to 69.26%)	100.0%		2.66 (2.04 to 3.35)	82.9%	
Type of MI				**6×10^{-17}**			**0**			**6×10^{-8}**
Any	10	53.11% (26.72 to 77.87%)	99.3%		28.38% (11.58 to 54.53%)	99.9%		3.31 (2.84 to 3.85)	59.2%	
STEMI	2	23.84% (5.02 to 64.97%)	0.0%		11.28% (7.67 to 16.30%)	0.0%		2.46 (0.39 to 15.46)	0.0%	
NSTEMI	1	62.38% (59.64 to 65.04%)	-		45.60% (44.68 to 46.53%)	-		1.98 (1.75 to 2.23)	-	
Duration of follow up				0.0798			0.0974			0.5363
2 years or less	6	32.80% (17.65 to 52.66%)	87.4%		15.73% (6.33 to 34.02%)	99.1%		2.93 (2.33 to 3.70)	40.8%	
More than 2 years	7	62.21% (26.75 to 88.13%)	99.4%		37.65% (12.54 to 71.77%)	100.0%		2.65 (1.90 to 3.71)	85.0%	

ES – Effect size, OR – Odds ratio, CI – Confidence interval, MI – Myocardial infarction, STEMI – ST-elevation MI, NSTEMI – Non ST-elevation MI

[a]Predominantly Asian included all Asian race/ethnicity

[b]South Asia was not included in the analysis due to a lack of data.

[c]Lower middle-income group was not included in the analysis due to a lack of data.

Bolded values indicate p-value of <0.05 and it is taken as statistical significance.

Table 2. All-cause mortality outcomes following myocardial infarction, pooled and stratified by subgroups

		Underweight			Normal weight			Comparison of underweight against normal weight		
	Studies	**ES (95% CI)**	**I^2**	**p-value**	**ES (95% CI)**	**I^2**	**p-value**	**OR (95% CI)**	**I^2**	**p-value**
Overall	13	49.12% (28.46 to 70.08%)	99.3%		26.01% (12.82 to 45.66%)	100.0%		2.78 (2.30 to 3.35)	77.4%	**6×10^{-8}**
Race/Ethnicity[a]				0.1207			**0.0220**			**0.0062**
Predominantly Asian	6	34.49% (21.70 to 50.00%)	87.1%		13.67% (8.25 to 21.82%)	96.7%		3.56 (2.74 to 4.62)	26.1%	
Predominantly Caucasian	7	61.34% (23.74 to 88.99%)	99.5%		41.06% (13.60 to 75.51%)	100.0%		2.36 (1.80 to 3.09)	80.6%	
Region[b]				0.0768			**0.0113**			**0.0317**
East Asia & Pacific	5	31.74% (18.72 to 48.42%)	87.9%		12.46% (6.86 to 21.56%)	96.9%		3.51 (2.62 to 4.71)	39.0%	
Middle East & North Africa	1	53.85% (35.05 to 71.61%)	-		21.36% (18.31 to 24.77%)	-		4.30 (1.94 to 9.51)	-	
North America	4	76.44% (13.62 to 98.52%)	99.7%		57.72% (10.18 to 94.27%)	100.0%		2.41 (1.44 to 4.04)	89.4%	
Europe & Central Asia	3	37.52% (6.47 to 83.91%)	93.0%		22.14% (1.54 to 83.78%)	99.9%		2.26 (1.26 to 4.08)	26.0%	

Definition of underweight				**0.0046**			0.1350			0.7415
<18.5 kg/m^2	10	57.11% (30.81 to 79.92%)	99.3%		32.07% (13.81 to 58.19%)	100.0%		2.82 (2.26 to 3.52)	81.2%	
<20.0 kg/m^2	3	24.42% (15.84 to 35.67%)	0.0%		11.59% (5.20 to 23.85%)	92.0%		2.63 (1.16 to 5.94)	60.1%	
Retrospective/ Prospective				0.1862			0.1552			0.7982
Retrospective	3	62.77% (33.84 to 84.75%)	62.2%		42.74% (8.02 to 86.48%)	99.6%		2.95 (1.21 to 7.17)	75.2%	
Prospective	10	44.16% (20.29 to 71.07%)	99.4%		21.89% (8.73 to 45.09%)	100.0%		2.78 (2.24 to 3.45)	79.8%	
Income group[c]				0.2840			0.1751			0.8381
High	11	51.64% (27.16 to 73.56%)	99.4%		27.77% (11.95 to 52.13%)	100.0%		2.75 (2.24 to 3.38)	78.3%	
Upper middle	2	37.83% (3.20 to 91.81%)	68.8%		16.88% (8.77 to 30.03%)	61.0%		2.91 (0.10 to 86.37)	80.0%	
Single/ Multi Centre				0.6663			0.5866			0.2801

Single center	6	44.80% (30.62 to 59.89%)	74.6%		22.01% (11.01 to 39.18%)	99.4%		3.17 (2.31 to 4.35)	63.6%	
Multi center	7	52.86% (16.45 to 86.46%)	99.6%		29.83% (7.43 to 69.26%)	100.0%		2.66 (2.04 to 3.35)	82.9%	
Type of MI				**6×10^{-17}**			**0**			**6×10^{-8}**
Any	10	53.11% (26.72 to 77.87%)	99.3%		28.38% (11.58 to 54.53%)	99.9%		3.31 (2.84 to 3.85)	59.2%	
STEMI	2	23.84% (5.02 to 64.97%)	0.0%		11.28% (7.67 to 16.30%)	0.0%		2.46 (0.39 to 15.46)	0.0%	
NSTEMI	1	62.38% (59.64 to 65.04%)	-		45.60% (44.68 to 46.53%)	-		1.98 (1.75 to 2.23)	-	
Duration of follow up				0.0798			0.0974			0.5363
2 years or less	6	32.80% (17.65 to 52.66%)	87.4%		15.73% (6.33 to 34.02%)	99.1%		2.93 (2.33 to 3.70)	40.8%	
More than 2 years	7	62.21% (26.75 to 88.13%)	99.4%		37.65% (12.54 to 71.77%)	100.0%		2.65 (1.90 to 3.71)	85.0%	

ES – Effect size, OR – Odds ratio, CI – Confidence interval, MI – Myocardial infarction, STEMI – ST-elevation MI, NSTEMI – Non ST-elevation MI

[a]Predominantly Asian included all Asian race/ethnicity

[b]South Asia was not included in the analysis due to a lack of data.

[c]Lower middle-income group was not included in the analysis due to a lack of data.

Bolded values indicate p-value of <0.05 and it is taken as statistical significance.

Table 3. Secondary study outcomes and medications following myocardial infarction

		Underweight		Normal weight		Comparison of underweight against normal weight		
	Studies	**ES (95% CI)**	**I^2**	**ES (95% CI)**	**I^2**	**OR (95% CI)**	**I^2**	**p-value**
Secondary outcomes								
Cardiac mortality	5	18.71% (11.42 to 29.13%)	72.2%	8.41% (4.51 to 15.15%)	94.4%	2.70 (1.86 to 3.92)	57.3%	**0.0018**
In-hospital mortality	8	10.07% (9.73 to 10.42%)	58.4%	6.85% (4.26 to 10.84%)	97.0%	1.91 (1.84 to 1.99)	0.0%	**2×10^{-9}**
Any reinfarct	4	2.68% (0.27 to 21.78%)	90.9%	3.28% (0.62 to 15.58%)	98.6%	0.97 (0.76 to 1.22)	0.0%	0.6627
Nonfatal reinfarct	4	4.96% (1.46 to 15.53%)	72.5%	5.48% (1.91 to 14.73%)	96.6%	0.88 (0.41 to 1.88)	0.0%	0.6279
Cerebrovascular accident	4	3.55% (2.88 to 4.38%)	13.2%	1.38% (0.55 to 3.43%)	95.6%	1.24 (0.98 to 1.56)	27.0%	0.0627
Cardiogenic shock	3	6.97% (4.89 to 9.85%)	91.0%	5.53% (3.44 to 8.79%)	98.2%	1.11 (1.02 to 1.20)	54.1%	**0.0364**
Medications								
Aspirin	6	91.12% (63.64 to 98.37%)	99.3%	94.47% (75.98 to 98.93%)	99.9%	0.66 (0.62 to 0.71)	7.5%	**2×10^{-5}**
Clopidogrel	5	58.35% (6.33 to 96.67%)	95.6%	57.07% (8.39 to 95.08%)	99.9%	0.82 (0.70 to 0.95)	35.7%	**0.0186**
Beta blockers	9	65.48% (45.06 to 81.44%)	99.6%	71.09% (56.23 to 82.47%)	99.9%	0.76 (0.58 to 0.99)	91.2%	**0.0485**
ACEi/ARB	5	55.69% (55.69 to 83.00%)	89.6%	75.92% (60.10 to 86.83%)	98.6%	0.85 (0.73 to 0.99)	27.0%	**0.0444**
Statins	6	67.89% (44.46 to 84.82%)	92.5%	80.69% (60.75 to 91.86%)	99.1%	0.51 (0.39 to 0.66)	15.0%	**0.0012**

Glycoprotein IIb/IIIa inhibitors	3	38.84% (13.13 to 72.73%)	86.3%	45.80% (27.23 to 65.61%)	97.8%	0.64 (0.48 to 0.85)	22.6%	**0.0205**

ES – Effect size, OR – Odds ratio, CI – Confidence interval, ARB – Angiotensin receptor blocker, ACEi – Angiotensin-converting enzyme inhibitor

Bolded values indicate p-value of <0.05 and it is taken as statistical significance.

Table 3. Secondary study outcomes and medications following myocardial infarction

		Underweight		Normal weight		Comparison of underweight against normal weight		
	Studies	**ES (95% CI)**	**I^2**	**ES (95% CI)**	**I^2**	**OR (95% CI)**	**I^2**	**p-value**
Secondary outcomes								
Cardiac mortality	5	18.71% (11.42 to 29.13%)	72.2%	8.41% (4.51 to 15.15%)	94.4%	2.70 (1.86 to 3.92)	57.3%	**0.0018**
In-hospital mortality	8	10.07% (9.73 to 10.42%)	58.4%	6.85% (4.26 to 10.84%)	97.0%	1.91 (1.84 to 1.99)	0.0%	**2×10^{-9}**
Any reinfarct	4	2.68% (0.27 to 21.78%)	90.9%	3.28% (0.62 to 15.58%)	98.6%	0.97 (0.76 to 1.22)	0.0%	0.6627
Nonfatal reinfarct	4	4.96% (1.46 to 15.53%)	72.5%	5.48% (1.91 to 14.73%)	96.6%	0.88 (0.41 to 1.88)	0.0%	0.6279
Cerebrovascular accident	4	3.55% (2.88 to 4.38%)	13.2%	1.38% (0.55 to 3.43%)	95.6%	1.24 (0.98 to 1.56)	27.0%	0.0627
Cardiogenic shock	3	6.97% (4.89 to 9.85%)	91.0%	5.53% (3.44 to 8.79%)	98.2%	1.11 (1.02 to 1.20)	54.1%	**0.0364**
Medications								
Aspirin	6	91.12% (63.64 to 98.37%)	99.3%	94.47% (75.98 to 98.93%)	99.9%	0.66 (0.62 to 0.71)	7.5%	**2×10^{-5}**
Clopidogrel	5	58.35% (6.33 to 96.67%)	95.6%	57.07% (8.39 to 95.08%)	99.9%	0.82 (0.70 to 0.95)	35.7%	**0.0186**
Beta blockers	9	65.48% (45.06 to 81.44%)	99.6%	71.09% (56.23 to 82.47%)	99.9%	0.76 (0.58 to 0.99)	91.2%	**0.0485**
ACEi/ARB	5	55.69% (55.69 to 83.00%)	89.6%	75.92% (60.10 to 86.83%)	98.6%	0.85 (0.73 to 0.99)	27.0%	**0.0444**
Statins	6	67.89% (44.46 to 84.82%)	92.5%	80.69% (60.75 to 91.86%)	99.1%	0.51 (0.39 to 0.66)	15.0%	**0.0012**

Glycoprotein IIb/IIIa inhibitors	3	38.84% (13.13 to 72.73%)	86.3%	45.80% (27.23 to 65.61%)	97.8%	0.64 (0.48 to 0.85)	22.6%	**0.0205**

ES – Effect size, OR – Odds ratio, CI – Confidence interval, ARB – Angiotensin receptor blocker, ACEi – Angiotensin-converting enzyme inhibitor

Bolded values indicate p-value of <0.05 and it is taken as statistical significance.

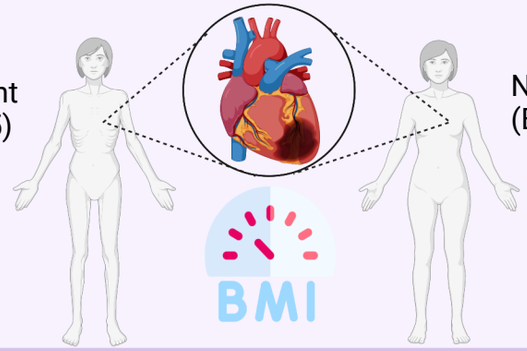
Central Illustration

Study Selection

Patients with MI were assessed for their BMI

Underweight (BMI < 18.5)

Normal weight (BMI 18.5 - 25.0)

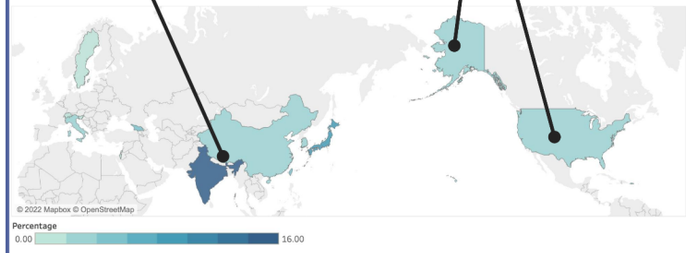


Prevalence

Of 6,368,225 patients with MI, **2.96%** were underweight

4.95% in Asian cohorts

1.84% in Caucasian cohorts



14.22%
Lower middle-income countries

3.40%
Upper middle-income countries

2.57%
High-income countries

Compared to normal weight patients, underweight patients:

Baseline Characteristics. Lower rates of:

Dyslipidemia
Underweight: 27.9%
Normal weight: 39.0%
p<0.0001

Diabetes mellitus
Underweight: 17.8%
Normal weight: 25.9%
p<0.0001

Hypertension
Underweight: 52.6%
Normal weight: 56.2%
p<0.0001

Prescribed fewer:

Statins
(OR: 0.51, CI: 0.39 - 0.66, p=0.0012)

Aspirin
(OR: 0.66, CI: 0.62 - 0.71, p<0.0001)

Glycoprotein IIb/IIIa inhibitors
(OR: 0.64, CI: 0.48 - 0.85, p=0.0205)

Beta-blockers
(OR: 0.76, CI: 0.58 - 0.99, p=0.0485)

Clopidogrel
(OR: 0.82, CI: 0.70 - 0.95, p=0.0186)

ACE-inhibitors/ARBs
(OR: 0.85, CI: 0.73 - 0.99, p=0.0444)

Outcomes. Increased rates of:

All-cause mortality
(HR: 1.66, CI: 1.44 - 1.92, p<0.0001)

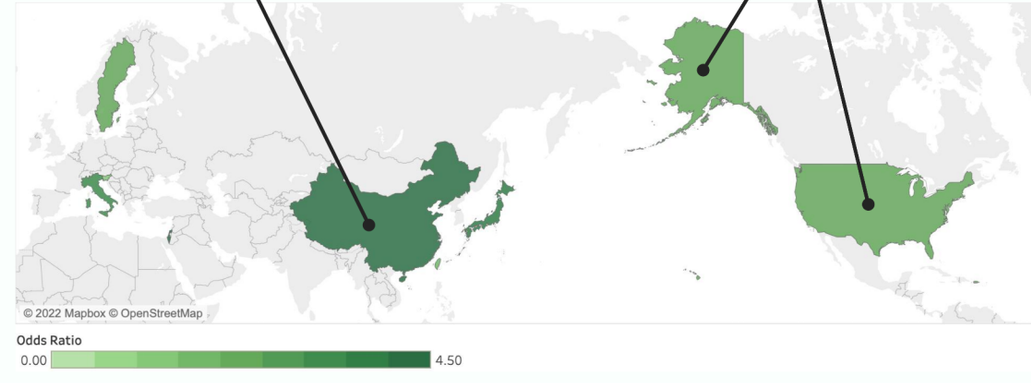
In-hospital mortality
(OR: 1.91, CI: 1.84 - 1.99, p<0.0001)

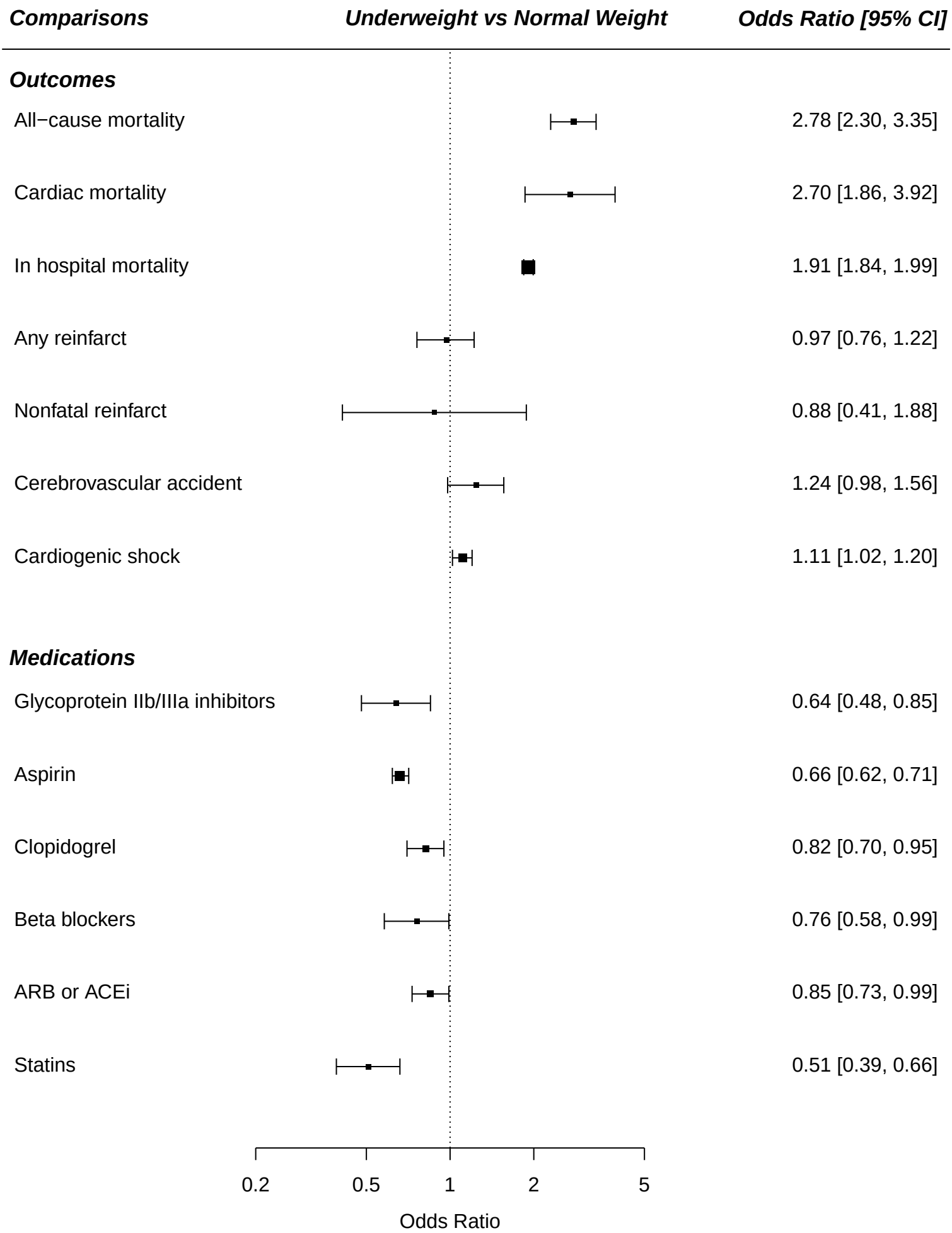
Cardiac mortality
(OR: 2.70, CI: 1.86 - 3.92, p=0.0018)

Cardiogenic shock
(OR: 1.11, CI: 1.02 - 1.20, p=0.0364)

Predominantly Asian cohorts
(OR: 3.56, CI: 2.74 - 4.62, p=0.0062)

Predominantly Caucasian cohorts
(OR: 2.36, CI: 1.80 - 3.09, p=0.0062)





Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Adrian Brown reports a relationship with Novo Nordisk Inc that includes: funding grants and speaking and lecture fees. Adrian Brown reports a relationship with Obesity UK that includes: speaking and lecture fees. Adrian Brown reports a relationship with PHE that includes: speaking and lecture fees. Adrian Brown reports a relationship with Medical Advisory Board that includes: board membership. Adrian Brown reports a relationship with Reset Health Clinics Ltd that includes: equity or stocks.