Relation of Body Mass Index Categories with Risk of Sudden Cardiac Death

A Systematic Review and Meta-Analysis

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Summary

The aim of this study was to evaluate the association of the body mass index (BMI) categories with the risk of sudden cardiac death (SCD) in a systematic review and meta-analysis.

We systematically searched the PubMed, Embase, and Cochrane Library databases up to February 2018 for all studies reporting an association between BMI and risk of SCD. Relative risks (RRs) and 95% confidence intervals (CIs) were extracted and pooled using a random effects model.

A total of 10 studies involving 1,381,445 participants were included in the meta-analysis. Overall, compared with the risk level in normal-weight controls, being underweight was not associated with increased risk of SCD (RR = 1.20, 95% CI, 0.95-1.51; $P = 0.13$). In contrast, both being overweight (RR = 1.21, 95% CI, 1.08-1.35; $P = 0.0008$) and obesity (RR = 1.52, 95% CI, 1.31-1.77; $P < 0.00001$) were associated with increased risk of SCD. The association between the BMI categories and risk of SCD was stable in the sensitivity analysis in which individual studies were serially excluded.

The findings from this meta-analysis indicate that excess weight is associated with an increased risk of SCD. Further research is required to explore the underlying mechanisms.

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Key words: Risk factor, Obesity, Overweight, Cardiovascular

Sudden cardiac death (SCD) is defined as unexpected natural death from a cardiac cause within a short time period, generally < 1 hour from the onset of symptoms, occurring despite resuscitation attempts in a person without any prior warning symptoms that would suggest a fatal condition.¹⁾ SCD is an important public health problem around the world and is associated with significant disability and morbidity.²⁾ Although implantable cardioverter-defibrillators are recommended by most guidelines for patients with the highest risk of SCD,^{3,4)} these patients account only for 25-30% of the entire population of SCD.^{5,6)} Moreover, ICD shocks can lead to arrhythmic storm, multiple shocks, and, eventually, death. Hence, it is necessary to explore the optimal therapy, including understanding the modifiable risk factors for the prevention of SCD.

ous cardiovascular diseases.^{8,9)} Epidemiological data on the relationship between obesity and risk of SCD are somewhat conflicting, although some studies have reported a positive association between obesity and risk of SCD.^{5,10-13)} Nevertheless, other studies attempting to address this issue yielded inconsistent results. Body mass index (BMI) is recommended as a measure to evaluate a person's weight condition. In the past few years, a plethora of studies have indicated that an elevated BMI is not significantly associated with overall SCD risk.¹⁴⁻¹⁷⁾ Considering the high prevalence of obesity in the general population and the ongoing controversy surrounding this problem, illuminating the relationship between BMI and risk of SCD will provide evidence for decision-making in clinical practice. Although obesity was associated with an increased risk of SCD in a previous meta-analysis by Agbaedeng, *et al*,¹⁸⁾ whether being overweight also increases this risk remains unclear. In addition, there were several limitations to this meta-analysis,¹⁸⁾ having a significant heterogeneity across the included studies, and published in an abstract form. Since then, a recent prospective study¹³⁾ has reported an increase in the risk of SCD among overweight patients. Therefore, we conducted a systemic review and meta-analysis to investigate the relationship between BMI cate-

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Recently, several potential risk factors including diabetes mellitus, chronic kidney disease, depression, and electrocardiogram abnormalities have been found to be related to SCD.¹⁾ Obesity is the most common nutritional disorder⁷⁾ and a widely acknowledged risk factor for vari-

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gories and risk of SCD.

Methods

In this meta-analysis, the data are presented in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology protocol (MOOSE)¹⁹⁾ and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.²⁰⁾ Since this study was a systematic review and meta-analysis, no patients were involved in setting the research question, the outcome measures, the design, or the implementation of this study.

Search strategy: Using electronic retrieval methods, we systematically searched the PubMed, Embase and Cochrane Library databases up to February 2018, with no language restrictions, for all studies that examined and reported the association between BMI categories and the risk of SCD. We performed the searches with the following keywords and subject terms: 'body mass index', 'body weight', 'obesity', 'overweight', 'central obesity', 'sudden death', and 'sudden cardiac death'. The search was limited to studies of human subjects. Additionally, we searched the reference lists of the retrieved studies for potentially relevant studies.

Study selection: Clinical studies were considered to be eligible if they met the following inclusion criteria: (1) they were published retrospective or prospective cohort studies that investigated the association between BMI categories and SCD; (2) adjusted relative risks (RRs) with 95% confidence intervals (CIs) were available; and (3) the studies that calculated BMI using the equation (calculated by weight (kg)/height (m)²) and defined the body mass categories established by the standard World Health Organization²¹⁾ as underweight (BMI < 18.5 kg/m²), normal weight (BMI of 18.5 to 24.9 kg/m²), overweight (BMI of 25.0 to 29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) or defined BMI categories according to the percentiles for age and sex established by the U.S. Centers for Disease Control and Prevention²²⁾ as less than 5th percentile (underweight), 5th to 24th percentile (reference group), 85th to 94th percentile (overweight), and 95th percentile or higher (obesity). Reviews, editorials, letters, abstracts, animal studies and duplicate data or unpublished data in studies were excluded from this meta-analysis.

Data extraction: Two independent reviewers (C-H and D-YQ) screened the titles and abstracts to select the relevant studies, and then, all data were extracted from each study separately using the aforementioned inclusion criteria. Any disagreements were resolved by discussion between the two reviewers or by a third reviewer (L-SH). The following elements were recorded for each study: name of the first author, year of publication, study design, study location, total number of participants, number of SCD, proportion of female participants, age at baseline, length of follow-up, BMI assessment and BMI categories.

Quality assessment of included studies: The Newcastle-Ottawa scale (NOS) was used to appraise the quality of the prospective studies. This scale assigns a total score of up to 9 stars according to the selection of cohorts, comparability of cohorts, and assessment of outcomes.²³⁾ We de-

finer studies with an NOS score ≥ 6 stars as moderate to high quality and studies with an NOS score < 6 stars as low quality.²⁴⁾

Data synthesis and analysis: All data were analyzed quantitatively with the software Review Manager (RevMan) version 5.30 (the Nordic Cochrane Center, Rigshospitalet, Denmark; <http://ims.cochrane.org/revman>). The effect measurement estimate chosen was the relative risk (RR) and corresponding 95% confidence interval (CI). The natural logarithm of the RR (logRR) and its standard error (SElogRR) were calculated and then pooled using statistical software. Potential heterogeneity was evaluated by using the I² statistic, with values of 25%, 50%, and 75% representing low, moderate, and notable heterogeneity, respectively. Because of the heterogeneous nature of the included studies, we used random- rather than fixed-effects models to estimate the pooled RRs more conservatively.²⁴⁾ To assess the influence of individual studies on the pooled data, we conducted sensitivity analysis when appropriate. According to the Cochrane book, the publication bias was tested by a funnel plot. Therefore, we did not test the publication bias in this meta-analysis. A value of *P* < 0.05 was considered statistically significant.

Results

Search selection: The detailed steps of the electronic database search are shown in Figure 1. We initially retrieved 4,037 records (1,653 through PubMed, 2,011 through Embase, and 373 through the Cochrane Library) using the search strategy. After removal of duplicate studies, the titles and abstracts of the remaining 3,632 articles were screened. Through the manual screening process, 3,615 articles were excluded. Of the remaining 27 studies, we excluded 7 studies after reading the full text: 6 articles were excluded because they did not regard BMI as a categorical variable, and 1 article²⁵⁾ was excluded because it was published only in abstract form. Ultimately, 10 prospective studies^{5,10-17,26)} were included in this meta-analysis.

Characteristics of included studies: The 10 studies^{5,10-17,26)} included a total of 1,381,445 participants and ranged in duration from 3.5 years to 56 years. All 10 studies were performed with a prospective design. Among these studies, 1 study¹³⁾ was from an Israeli national database, 2 studies^{15,17)} were conducted in Japan, and 7 studies^{5,10-12,14,26)} were conducted in Europe or North America. The proportion of females ranged from 0% to 100%. The study by Gastellurrutia, *et al.*¹⁴⁾ was conducted in patients with heart failure, while the rest were community studies. BMI categories were defined according to the statement from the U.S. Centers for Disease Control and Prevention in the study by Twig, *et al.*,¹³⁾ while the others were based on the standard of the World Health Organization. The basic characteristics of the included studies are given in the Table.

Study quality assessment: The NOS scores of the 10 studies selected for this meta-analysis are shown in the Supplemental Table. Overall, the quality of all included studies was good, with a score range of 7-9, and there was no high risk of potential bias.

Figure 1. PRISMA diagram of the study selection process for the meta-analysis. PRISMA indicates Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table. Characteristics of the 10 Included Studies

Study (first author, year)	Study design	Country	Included groups	Number	Age (y)	Follow-up (y)	Female (%)	Incidence of SCD
Adabag S, 2015 ¹⁰⁾	Prospective	USA	Community study	14,941	54.2	12.6	55	1.69%
Albert CM, 2003 ⁵⁾	Prospective	USA	Community study	121,701	-	22.0	100	0.20%
Chiuve SE, 2015 ¹¹⁾	Prospective	USA	Community study	72,484	45.7	26.0	100	0.61%
Eranti A, 2016 ¹²⁾	Prospective	Finland	Community study	10,169	44.1	6.0	46.9	7.29%
Twig T, 2016 ¹³⁾	Prospective	Israel	Community study	903,747	-	17.6	-	0.04%
Gastelurrutia P, 2011 ¹⁴⁾	Prospective	Spain	Patients with HF	979	64.4	3.7	27.5	8.89%
Ohira T, 2011 ¹⁵⁾	Prospective	Japan	Postmenopausal women	954	66.2	3.5	41.8	0.89%
Bertoia ML, 2012 ¹⁶⁾	Prospective	USA	Community study	161,808	62.6	10.8	100	0.26%
Chei CL, 2008 ¹⁷⁾	Prospective	Japan	Community study	90,679	-	9.7	47.7	0.01%
Cuddy TE, 2006 ²⁶⁾	Prospective	Canada	Community study	3,983	31	56	0	4.29%

HF indicates heart failure; y, years; and SCD, sudden cardiac death.

Data analysis: Underweight versus normal weight Three studies^{10,13,15)} including 628,375 participants (150,697 underweight participants and 477,678 normal participants) compared the risk of SCD between normal-weight and underweight groups. As shown in Figure 2, compared with normal weight, underweight did not increase the risk of SCD (RR = 1.20, 95% CI, 0.95 to 1.51; $P = 0.13$). We did not find any heterogeneity across the included studies ($I^2 = 0$, $P = 0.83$).

Overweight versus normal weight Nine studies^{5,10-17)} described the association between overweight and SCD. As presented in Figure 2, compared with normal weight, overweight was significantly associated with an increased risk of SCD (RR = 1.21, 95% CI, 1.08-1.35; $P = 0.0008$), with a low heterogeneity across the included studies ($I^2 = 8\%$, $P = 0.37$). One study¹⁴⁾ was conducted in patients with heart failure, and we therefore re-performed this analysis after removing this study. Consequently, we ob-

Figure 2. Forest plot of the association between body mass index and sudden cardiac death. IV indicates inverse variance; and SE, standard error.

served a similar result, with an RR of 1.20 in healthy overweight individuals compared with normal-weight individuals (95% CI 1.06 to 1.36; $P = 0.005$) (Supplemental Figure). Heterogeneity was low across the included studies ($I^2 = 20\%$, $P = 0.27$).

Obesity versus normal weight Compared with normal-weight participants, obese participants had an elevated risk of SCD in 5 studies,^{5,11-13,26} whereas the other studies^{10,14-17} showed an inconsistent conclusion. The pooled analysis showed that obesity was significantly associated with an elevated SCD risk (RR = 1.52, 95% CI, 1.31-1.77; $P < 0.00001$; Figure 2). There was a moderate heterogeneity across these studies ($I^2 = 30\%$, $P = 0.17$). Similarly, after removing one study that included participants with heart failure,¹⁴ we found that obesity increased the risk of SCD (RR = 1.58, 95% CI, 1.39-1.80; $P < 0.00001$), with low heterogeneity across studies ($I^2 = 12\%$, $P = 0.34$) (Supplemental Figure).

Publication bias and sensitivity analysis: Publication bias was assessed by subjective determination of funnel plot asymmetry. A funnel plot (Figure 3) suggested the absence of major publication bias. The association between BMI and SCD was stable in the sensitivity analysis in which studies were excluded one by one. Specifically, the association between BMI and SCD was robust after we removed the study by Twig, *et al.* in which BMI categories were defined according to the U.S. Centers for Disease Control and Prevention,¹³ or the study by Gastelurrutia, *et al.* conducted in patients with heart failure.¹⁴ Similar results were also observed in this meta-analysis after using a random-effects model to estimate the pooled RRs.

Discussion

In the present meta-analysis, we first fully examined the association between BMI level and the risk of SCD.

Figure 3. Funnel plot of the association between body mass index and sudden cardiac death. RR indicates risk ratio; and SE, standard error.

On the basis of the predefined inclusion criteria, a total of 10 prospective studies with 1,381,445 participants were selected and assessed in the final analysis. Our analysis indicates that being obese has a positive association with the risk of SCD, which is consistent with a previous meta-analysis by Agbaedeng, *et al.*¹⁸⁾ In addition to obesity, being overweight is also associated with an increased risk of SCD. Moreover, these associations were stable in a sensitivity analysis in which studies were excluded one by one.

Many studies have demonstrated an association between obesity and various cardiovascular diseases, including coronary heart disease, stroke, and heart failure.^{8,9)} Obesity also increases the risks of dyslipidemia,²⁷⁾ type 2 diabetes,²⁸⁾ and hypertension.²⁷⁾ In addition, excess weight can lead to hemodynamic changes that impair cardiac structure and function.²⁹⁾ Being overweight or obesity has been associated with increased risks of all-cause mortality³⁰⁾ and cardiovascular disease.³¹⁾

Being underweight is also related to an increased risk of all-cause mortality.³²⁾ Being underweight is a marker of severe disease and is associated with deficits in immune function, tissue function, and other functions.³³⁾ However, we found no association between being underweight and the risk of SCD in the current study. Because of the limited number of studies included here, more data are needed to confirm this association of underweight and risk of SCD.

Recently, several studies have investigated the association between BMI level and the risk of SCD, which remains unclear owing to the inconsistent results. In the present study, we found that obesity or being overweight was correlated with an increased risk of SCD. Recent data also

suggest that excess body weight is an independent risk factor for ventricular arrhythmias and SCD in patients with sudden cardiac arrest,³⁴⁾ in patients with ischemic cardiomyopathy,³⁵⁾ and even in patients without heart failure.³⁶⁾ SCD in middle-aged adults is independently and significantly associated with obesity.³⁴⁾ In the Multicenter Automatic Defibrillator Implantation Trial-II,³⁵⁾ obesity increased the risks of appropriate ICD intervention by 64%, appropriate shock by 86%, and VT/VF or sudden cardiac death by 59% in patients with ischemic cardiomyopathy. Compared with the lean body condition, obesity is also associated with an increased risk of premature ventricular (but not atrial) contractions.³⁶⁾

The potential mechanisms of overweight-related and obesity-related SCD remain unclear. Recently, a study by Finocchiaro, *et al.* explored the burden and etiologies of SCD in young (< 35 years of age) obese individuals and has shown various conditions underlying SCD in obesity including sudden arrhythmic death syndrome, left ventricular hypertrophy and coronary artery disease.³⁷⁾ The mechanisms that underlie the development of SCD in overweight or obese patients are complicated. Many factors have been suggested to explain the increased risk of SCD in these patients, such as left ventricular hypertrophy,³⁸⁾ increased electrical irritability,³⁹⁾ and autonomic deregulation.⁴⁰⁾ Left ventricular hypertrophy is a common finding in overweight or obese patients and is associated with an increased risk of SCD.⁴¹⁾ The hearts of obese individuals display pathological myocardial changes including myocyte hypertrophy, fibrosis, focal myocardial disarray, fatty and mononuclear cell infiltration, and increased epicardial fat.⁴²⁾ Substantial evidence supports an increased

electrical irritability in obesity. Histological studies have also shown pathologic changes involving the conduction system in young, obese subjects with SCD.⁴³⁾ Obesity is associated with a great number of electrocardiogram abnormalities, including QRS fragmentation,³⁹⁾ prolongation of the QT interval,⁴⁴⁾ and ventricular late potentials,⁴⁵⁾ which indicate an increased propensity to suffer from SCD. Functional abnormalities of voltage-gated potassium channels⁴⁴⁾ and calcium channels⁴⁶⁾ have been reported in obese animal models and may lead to increased vulnerability to early afterdepolarization and lethal ventricular arrhythmias.

Our meta-analysis confirmed the findings of a previous meta-analysis by Agbaedeng, *et al.*¹⁸⁾ that obesity increased the risk of SCD. Furthermore, we first proposed that being overweight is also associated with an increased risk of SCD. With the growing prevalence of being overweight and obesity, these findings have important implications in the prevention of SCD. Although obesity and being overweight are associated with an increased risk of SCD, it is less clear what role waist circumference and waist-to-hip ratio have. Excess abdominal fat has been associated with the risks of various cardiovascular diseases.⁴⁷⁾ Recently, 2 studies^{10,16)} investigated the association between waist-to-hip ratio and SCD, but the results are conflicting.

Study limitations: Several limitations may affect the validity of this meta-analysis. First, although we chose RR as the risk estimate and most of the included studies adjusted for a range of confounding variables, we could not exclude the effects of residual confounders that may have had an impact on the results. Second, all the included studies were observational studies. The findings may therefore have been influenced by selection bias, attrition bias or other factors present in observational studies. Third, the classification of SCD may affect the relationship between BMI category and SCD. Unfortunately, a subgroup analysis based on the classification of SCD could not be performed owing to the limited data. Finally, we reported only the correlation of SCD with BMI and not with other aspects of body composition, such as visceral fat or fat distribution. BMI does not distinguish between weight associated with muscle and weight associated with fat. The influence of waist circumference or waist-to-hip ratio on SCD needs to be investigated in the future.

Conclusions

In conclusion, this meta-analysis indicates that being obese or overweight are associated with an increased risk of SCD. Further research is required to confirm these findings and understand the underlying mechanism of this association.

Disclosures

Conflicts of interest: None declared.

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Supplemental Files

Supplemental Table

Supplemental Figure

Please see supplemental files; <https://doi.org/10.1536/ihj.18-155>