

1 **Title: Sudden Death in Obesity: Mechanisms and Management**

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27

28 **Abstract**

29 In recent decades, the prevalence of obesity has increased significantly, leading to an epidemic at  
30 the global level. Obesity is associated with various metabolic alterations and increases the risk of  
31 cardiovascular disease (CVD). The most devastating manifestation of CVD is sudden cardiac  
32 death (SCD), leading to substantial years of potential life lost worldwide. Obesity-related SCD is  
33 an increasingly important public health problem and warrants a specific investigative focus on  
34 improved risk stratification and prevention. In this review article, we summarize the current  
35 evidence regarding management of SCD in obesity and discuss knowledge gaps as well as future  
36 directions in this field.

37

38 **Condensed abstract**

39 Obesity is a significant risk factor for cardiovascular diseases and most of the obesity-related  
40 premature deaths are due to cardiovascular causes. Approximately half of all deaths due to  
41 cardiac causes are sudden cardiac deaths (SCD). Obesity and especially visceral fat increase the  
42 risk of SCD, and obesity-associated SCD is often accompanied by cardiac hypertrophy and  
43 CAD. However, the proximate causes and risk markers of SCD in obesity are not well  
44 understood, and future studies are also warranted to investigate the effect of weight loss and  
45 obesity therapies on SCD risk.

46

47 **Abbreviations**

48 BMI: body mass index, CAD: coronary artery disease, CPAP: continuous positive airway  
49 pressure, CT: computed tomography, EF: ejection fraction, GLP: glucagon-like peptide, HF:  
50 heart failure, ICD: implantable cardioverter defibrillator, LVH: left ventricle hypertrophy, MI:  
51 myocardial infarction, OSA: obstructive sleep apnea, SCA: sudden cardiac arrest, SAD: sagittal  
52 abdominal diameter, SCD: sudden cardiac death, VA: ventricular arrhythmia, WC: waist  
53 circumference, WHR: waist-to-hip ratio

## 54 **Background and Introduction**

### 55 **Definitions**

#### 56 *Sudden Cardiac Death*

57 Sudden cardiac death (SCD) is generally defined as a death due to cardiac causes that occurs  
58 suddenly and unexpectedly (1). SCD has been estimated to account for about half of all  
59 cardiovascular deaths (2), with an estimated annual US incidence of approximately 360,000 (3).  
60 The critical event is sudden cardiac arrest (SCA) which is mostly lethal since only about 10%  
61 survive (4). Therefore, prediction and prevention of SCA are the most important measures to  
62 reduce premature mortality from SCD.

63 In the vast majority of individuals, SCD is a multifactorial and complex event that can involve  
64 multiple underlying substrates and maintainers of lethal ventricular arrhythmias (e.g., coronary  
65 artery disease [CAD], cardiac hypertrophy) and acute triggers (e.g., ischemia, hypoxia, and  
66 electrolyte imbalance)(5, 6). The most important underlying substrate for SCD in the general  
67 population is CAD and ischemic cardiomyopathy, accounting for approximately 70-80% of all  
68 subjects (7, 8, 9). SCD may strike at any age, but the mean age of SCD cases is 60-70 years, and  
69 the prevalence of CAD starts to increase in the fourth decade (7, 8). Among younger SCD  
70 victims, inherited cardiomyopathies, arrhythmia syndromes, and structurally normal findings  
71 prevail in post-mortem investigations (10).

#### 72 *Obesity*

73 Obesity is a condition where there is an excessive accumulation of body fat. In the majority of  
74 individuals, obesity develops due to a chronic mismatch in energy intake and consumption and is  
75 most often defined as body mass index (BMI)  $\geq 30\text{kg/m}^2$ . Severe obesity (Class 2) and morbid

76 obesity (Class 3) are defined as  $BMI \geq 35 \text{ kg/m}^2$  and  $BMI \geq 40 \text{ kg/m}^2$ , respectively(11). However,  
77 BMI does not directly measure body composition and in some instances, high BMI may result  
78 from high muscle mass or water retention. Body fat is usually distributed around visceral organs  
79 or subcutaneously, and visceral fat is metabolically more active and more strongly associated  
80 with increased overall mortality (12), as well as SCD (13). More specific measurements for  
81 estimating visceral fat are waist circumference (WC), waist-to-hip ratio (WHR), and sagittal  
82 abdominal diameter (SAD). The amount of body fat can also be assessed with various body  
83 composition measurements (e.g., bioimpedance), but the current literature lacks comprehensive  
84 studies using such measures in assessing the risk of SCD.

85 In 1998, the National Institutes of Health classified obesity as a complex multifactorial chronic  
86 disease(14). Obesity is associated with approximately 4 years lower life expectancy(15), and  
87 more than two-thirds of obesity-related deaths are due to cardiovascular causes(11) (Figure 1).  
88 According to the Global Burden of Disease, over 4 million people die annually because of being  
89 overweight or obese(16). During the last two decades, the prevalence of obesity has increased  
90 from 30.5% to 41.9% among adults aged 20 and over in the U.S.(17). Given the high population  
91 prevalence, obesity is associated with a high population-attributable fraction of cardiovascular  
92 diseases and SCD (18).

93

## 94 **Epidemiological Evidence Linking Obesity to Sudden Cardiac Death**

### 95 ***BMI and SCD***

96 Several epidemiological studies have investigated the relationship between BMI and the risk of  
97 SCD. The balance of evidence suggests a significantly increased risk of SCD associated with

98 obesity. A meta-analysis demonstrated that every 5-unit increment in BMI is associated with a  
99 16% increased risk of SCD (19). The risk is highest among those with high BMI but is also  
100 increased among those with low BMI, creating a J-shape association between BMI and the risk  
101 of SCD.

### 102 *Obesity and the proportional risk of SCD*

103 Early studies reported that the proportion of SCD in CAD-related deaths was increased in obese  
104 individuals (20, 21) but findings in more recent studies have been mixed. The proportional risk  
105 of SCD and obesity was investigated in heart failure (HF). A recent study developed prognostic  
106 models for arrhythmic and non-arrhythmic mortality among 4,531 patients with left ventricle  
107 dysfunction due to CAD (enrolled in the MADIT trials) and found that low BMI predicted non-  
108 arrhythmic mortality more than arrhythmic mortality (22). Somewhat similar results were found  
109 in a cohort of 9,885 HF patients without ICDs, in which higher BMI was independently  
110 associated with a greater proportional risk of sudden death (23). However, another report from  
111 the general population suggested that the risk for non-sudden cardiac mortality is similarly  
112 increased in obesity (24). This finding is supported by data from the 1986 National Mortality  
113 Followback Survey and the U.S. Bureau of the Census, in which there were no differences in  
114 BMI between SCD and non-SCD CAD deaths (25). Since the prevalence of obesity continues to  
115 rise, more studies using consistent definitions of obesity are needed.

### 116 *Visceral Obesity*

117 When compared to BMI, visceral obesity has been associated more strongly with increased risk  
118 of SCD. The meta-analysis by Aune et al found that a 0.1 unit increase in waist-to-hip ratio was  
119 associated with an 82% increased risk of SCD (19). Increased SCD risk in visceral obesity has

120 been demonstrated in both sexes. In the Paris Prospective Study, the risk of SCD increased  
121 proportionally with SAD level, and individuals in the highest SAD quintile had a 2.6-fold higher  
122 risk of SCD in comparison to those in the lowest SAD quintile(26). Similarly, a study by Bertoia  
123 et al investigated 161,808 women from across the U.S. and found that the highest WHR quartile  
124 was associated with a 73% increased risk of SCD(27). WHR had the greatest population-  
125 attributable fraction for SCD along with hypertension and myocardial infarction (MI). Data from  
126 the Nurses' Health Study suggested that abdominal obesity is associated with elevated  
127 cardiovascular mortality even among those with normal BMI(28).

### 128 *Obesity paradox*

129 The obesity paradox refers to several observations which have demonstrated that in the elderly,  
130 and patients with chronic diseases, (e.g., heart failure or CAD), overweight or mild obesity may  
131 be protective and is associated with higher survival (29). Primary prevention ICD is currently  
132 recommended for HF patients with EF<35%, and the obesity paradox has also been shown to  
133 apply in HF patients with an ICD (30). The reasons for the obesity paradox are not fully clear.  
134 Potential explanations include lead time bias (patients with obesity may develop cardiac disease  
135 earlier in their lifetime), cardiac cachexia (patients with low BMI and unintentional weight loss  
136 have a high mortality rate), and lower comorbidity burden, which may result from an earlier age  
137 at the time of cardiac disease diagnosis (11).

138 In the sudden cardiac arrest setting, obesity may influence the underlying etiologies and  
139 presenting rhythm, and create special challenges that may impact resuscitation efforts and  
140 survival rates. Some studies have found that patients with obesity have a worse prognosis in out-  
141 of-hospital cardiac arrest (31, 32). For example, data from the Swedish Registry of  
142 Cardiopulmonary Resuscitation showed that obesity was associated with a 31% decrease in

143 survival, which further decreased by 45% when obesity was accompanied by diabetes (32).  
144 Other studies have however found different results, and there is no clear evidence of whether  
145 obesity affects the chances of survival after cardiac arrest (33, 34).

#### 146 **Clinical Antecedents of Obesity-Related SCD**

147 Obesity increases the risk of traditional cardiovascular risk factors, which are also important  
148 mediators of SCD risk. The risk of type 2 diabetes is increased by approximately 10-fold (35, 36,  
149 37), CAD by ~5-fold (29, 35, 38), hypertension by ~3-fold (38, 39), and dyslipidemia by ~2-fold  
150 (39) in obese patients. More than half of obese patients have metabolic syndrome(40, 41, 42),  
151 which is defined as having 3 or more metabolic syndrome components (high blood pressure,  
152 high plasma triglycerides, low high-density lipoprotein cholesterol, high fasting blood glucose,  
153 and abdominal obesity)(43). Although metabolic syndrome is usually treated as a dichotomous  
154 variable, the relationship between metabolic syndrome components and cardiovascular disease is  
155 more likely to be a continuum, with a higher burden of component conditions corresponding to a  
156 higher risk of SCD (44).

#### 157 ***Is Obesity an Independent Risk Marker for SCD?***

158 Despite the confounding effect of metabolic abnormalities, obesity has also been associated with  
159 an increased risk of SCD independently from other conventional cardiovascular risk factors. In  
160 the ARIC study, abdominal obesity was associated with a 2-fold increased risk of SCD  
161 independently from hypertension, diabetes, abnormal lipid levels, prevalent CAD/heart failure,  
162 resting heart rate, and ECG-LVH (13). Another study of a general population sample of 10,543  
163 middle-aged subjects found that BMI  $\geq 30$  kg/m<sup>2</sup> was associated with a 79% increase in SCD risk  
164 after adjustment for age, sex, smoking, blood pressure, diabetes, cholesterol, baseline cardiac

165 disease, and ECG abnormalities (24). Data from the Paris Prospective study and the Nurses'  
166 Health Study also demonstrated that obesity is an independent risk factor for SCD, but,  
167 interestingly, not for fatal MI/CAD (28, 45, 46). Moreover, data from the Paris Prospective study  
168 showed that abdominal obesity increases the risk of SCD regardless of BMI, and the association  
169 was stronger between abdominal obesity and SCD than between abdominal obesity and fatal MI  
170 (26) (Figure 2).

171 These findings indicate that obesity, and especially visceral obesity, may also increase the risk of  
172 SCD independent of CAD. A study of 2,185 middle-aged men reported somewhat contradictory  
173 findings, suggesting that metabolically healthy overweight/obese are not at an increased risk of  
174 SCD (47). However, this study of a relatively small, poorly powered sample combined  
175 overweight (BMI 25-30 kg/m<sup>2</sup>) and obese individuals. Larger meta-analyses have reported that  
176 metabolically healthy obese individuals are at an increased risk for cardiovascular events and  
177 overall mortality(48, 49). Metabolically healthy obesity may represent a “honeymoon phase” of  
178 obesity, with the majority of individuals developing metabolic abnormalities during follow-up  
179 (40, 41).

### 180 ***Physical Activity and SCD***

181 In addition to metabolic abnormalities, low exercise capacity may also confound increased SCD  
182 risk in obesity. Low exercise capacity predicts SCD (50), and data from a cohort of 2,357  
183 middle-aged men suggested that high BMI was not associated with SCD after adjustment for  
184 peak oxygen uptake (51). The interaction between BMI and exercise capacity is also likely to be  
185 complex since high BMI in physically active individuals may result from increased muscle mass  
186 instead of adipose tissue. Measures of visceral obesity (e.g. WC, WHR, SAD) would probably  
187 provide more accurate estimations of the interaction between physical activity and obesity-

188 related SCD risk. The direct exercise capacity test provides an accurate estimation of fitness, but  
189 it does not quantify the amount of weekly physical activity that could attenuate the excess of  
190 obesity-related cardiovascular risk. Of note, a study of 116,564 women found that high physical  
191 activity (>3.5h of exercise per week) did not eliminate the increased risk of overall death from  
192 obesity(52). Further studies are needed to evaluate the interaction between cardiorespiratory  
193 fitness, weekly physical activity, abdominal obesity, and SCD risk in more detail.

## 194 **Clinical Characteristics and Autopsy Findings**

### 195 *Prevalence of Obesity in SCD cohort studies*

196 Several autopsy series and community-based SCD cohorts have reported that younger SCD  
197 victims have a high prevalence of comorbid obesity (53, 54, 55, 56, 57, 58). In the Oregon SUDS  
198 study, the prevalence of obesity was 24% in SCD cases <25 years, and as much as 50% in SCD  
199 cases 25-34 years(54). Similarly, an SCD registry from Australia showed that 55% of cases 18-  
200 50 years of age were obese (56); significantly higher in comparison to the age-matched general  
201 population (29%,  $p<0.001$ ) and associated with high frequency of conventional cardiovascular  
202 risk factors. In the Fingesture study, 40% of SCD cases <40 years were obese (57), but  
203 somewhat lower estimates were reported from a nation-based cause-of-death registry in Sweden  
204 and a referral SCD cohort in the U.K., which a 15-20% prevalence of obesity among SCD  
205 victims <35 years of age (53, 58). The prevalence of comorbid obesity may be highest among  
206 young and middle-aged SCD cases. In the Oregon SUDS study, middle-aged SCD cases (35-60  
207 years) were more likely to have obesity in comparison to older SCD cases (48% vs 33%;  
208  $p<0.001$ )(59).

### 209 *Autopsy Findings in Obese SCD Cases*

210 In addition to accelerated atherosclerosis and CAD development, obesity leads to significant  
211 hemodynamic changes (e.g., higher blood volume) which promote cardiac hypertrophy,  
212 dilatation, heart failure, and ventricular arrhythmias (60, 61, 62, 63) (Figure 3). Studies on  
213 autopsy findings in obesity-related SCD have mainly focused on young individuals, and there is  
214 a lack of comprehensive autopsy reports on middle-aged and older obese SCD cases.

215 Current evidence indicates that the most common autopsy findings among obese SCD cases are  
216 cardiac hypertrophy and CAD when all age groups are included (56, 64, 65, 66, 67). Although  
217 obesity-related SCD often accompanies cardiac hypertrophy and dilatation, there has been some  
218 debate on whether obesity cardiomyopathy is a distinct entity, or whether cardiac remodeling in  
219 obesity is rather due to multiple comorbidities and metabolic alterations. In the Fingesture study,  
220 obesity-related hypertrophic cardiac disease (defined as cardiac hypertrophy, chamber dilatation,  
221 and excessive epicardial fat in individuals with BMI >30 in the absence of other explainable  
222 causes) was the most common non-ischemic autopsy finding among SCDs of all age groups (65).  
223 Moreover, autopsy studies of SCD cases from the U.K. and the U.S. also demonstrated that  
224 cardiomegaly is a common finding in obesity-related SCD even without concomitant CAD (67,  
225 68) (Figure 4).

226 While middle-aged and older SCD cases are often associated with structural cardiac  
227 abnormalities, young obese SCD cases may also present with structurally normal hearts at  
228 autopsy. The proportion of structurally normal hearts among obese SCD victims is however  
229 smaller than among their leaner counterparts (53, 54, 56, 69). In addition to cardiac hypertrophy,  
230 excessive epicardial fat is associated with an increased risk of ventricular arrhythmias in obesity  
231 (70) (Figure 5). The role of myocardial fat infiltration in arrhythmogenesis and obesity-related  
232 SCD is less well studied, but a small autopsy series of young obese SCD victims (n=7) found

233 that fat infiltration throughout the conduction system was present in 43%, and this finding was  
234 pronounced in markedly obese cases (71).

### 235 *Diurnal Variation and Presenting Rhythm in Obesity-Related SCD*

236 Obesity-related SCD is probably more likely to occur during nighttime hours than SCD in non-  
237 obese cases (72). This phenomenon could potentially be explained by a higher prevalence of  
238 obstructive sleep apnea (OSA) in obese individuals. In a cohort of 10,701 adults with  
239 polysomnograms followed for an average of 5.3 years, OSA was an independent predictor of  
240 SCD, and the magnitude of risk was dependent on the OSA severity, especially nocturnal O<sub>2</sub>  
241 saturation (73). Previous studies have also demonstrated that OSA increases especially the risk of  
242 nighttime SCD (74) and that continuous positive airway pressure (CPAP) management decreases  
243 the VA burden (75) (Figure 6).

244 OSA may increase the risk of arrhythmia and SCD through multiple mechanisms. Apnea may  
245 function as an SCD trigger by inducing parasympathetic activation and bradyarrhythmias with a  
246 higher likelihood of non-shockable SCD (76). Prior studies have also shown that non-shockable  
247 SCD is more likely to occur during nighttime hours than shockable SCD (77, 78). On the other  
248 hand, hypoxemia increases sympathetic activation when apnea terminates, which may in turn  
249 increase heart rate and blood pressure. This could trigger VAs due to coronary ischemia,  
250 especially in the presence of CAD (79). The prevalence of previously diagnosed OSA was not  
251 higher in nighttime SCD in the Oregon SUDS study (72), but this finding may be confounded by  
252 the under-diagnosis of OSA.

253 The existing literature also suggests that obesity may have a stronger association with non-  
254 shockable rhythms. A large cardiac arrest registry from Sweden demonstrated that the proportion

255 of shockable rhythm was lower in obese subjects (32). We have also recently developed an AI  
256 model to distinguish SCD cases presenting either ventricular fibrillation or pulseless electrical  
257 activity (80). This model identified high weight as a predictor of SCD presenting as pulseless  
258 electrical activity, further supporting the association between obesity and non-shockable SCD.

### 259 *Electrocardiographic Abnormalities in Obese SCD Victims*

260 There has been significant interest in identifying SCD risk markers from 12-lead ECG in  
261 anticipation of improving long-term risk stratification (81, 82, 83). Several depolarization and  
262 repolarization abnormalities have been associated with an increased risk of SCD in the general  
263 population, but the electrocardiographic signal is deteriorated by subcutaneous fat, which may  
264 complicate the application of ECG-based risk scores in obese patients(24). Accordingly, obese  
265 individuals have reduced sensitivity for ECG-based LVH, prolonged QTc interval, and leftward  
266 axis shifts (84).

267 There is a shortage of studies investigating SCD risk markers from the resting ECG in obese  
268 individuals. Data from Oregon SUDS showed that obese/overweight SCD cases had a  
269 significantly higher prevalence of QRS fragmentation in comparison to controls (85). A  
270 fragmented QRS complex may be a surrogate marker of conduction disturbances and delayed  
271 activation in the myocardium, which is again potentially a result of myocardial fibrosis or fat  
272 infiltration (86). Given the special considerations required for the analysis of ECGs in obese  
273 individuals, there is a need for a renewed focus on studies of ECG-based SCD risk markers in  
274 obesity.

275

### 276 **Potential Mechanisms of Lethal Arrhythmias in Obesity**

277 The specific pathways leading to lethal arrhythmias in obesity are not fully clear, but obesity is  
278 associated with several pathological alterations in cardiac structure and function which increase  
279 the risk of ventricular arrhythmias and SCD. These changes can be classified as electrical and  
280 structural remodeling of the heart, and due to the common underlying etiologies, the two may  
281 often co-exist.

### 282 *Electrical Remodeling*

283 Obese patients present with prolonged QTc interval, which has been associated with an increased  
284 risk of SCD in the general population (87, 88). For example, in the Oregon SUDS study,  
285 prolonged QTc was associated with a 5-fold risk of SCD (89, 90). Ventricular arrhythmias in  
286 acquired and inherited long QTc syndromes are thought to be precipitated by early  
287 afterdepolarizations, which are secondary voltage depolarizations during the repolarizing phase  
288 of the action potential. However, the effect of prolonged QTc on SCD risk may also be explained  
289 by prolonged depolarization. Recent data on large general population cohorts suggested that  
290 when the QTc interval is deconstructed into depolarization (QRS) and repolarization (JTc)  
291 intervals, the repolarization component may have no or only little independent prognostic value  
292 for SCD (91).

293 In obesity, increased adipose tissue leads to abnormally high expression of the aromatase  
294 enzyme, which converts testosterone to estrogens. While testosterone shortens the action  
295 potential, estrogens prolong the QTc interval by reducing the myocardial potassium channel  
296 current. The effect of adipose tissue on QTc lengthening is also supported by prior studies which  
297 have shown that QTc duration shortens significantly in response to weight loss after bariatric  
298 surgery (92). In addition to prolonged QRS and QTc intervals, other possible electrical triggers

299 for arrhythmogenicity in obesity are abnormal up-regulation of the sympathetic nervous system,  
300 increased heart rate, and decreased heart rate variability (93).

### 301 ***Structural Remodeling***

302 Obesity is often accompanied by cardiac hypertrophy and dilatation which are also common  
303 findings in post-mortem investigations of SCD. Increased heart weight develops in parallel with  
304 increased body size, and current guidelines recommend indexing cardiac chamber measurements  
305 to body surface area to allow comparison among patients with different body sizes (94).

306 However, structural remodeling in response to increased body size may also not be benign, and  
307 an absolute increase in cardiac hypertrophy has been associated with an approximately 3-fold  
308 increased risk of SCD (95, 96, 97). This excess risk is independent and additive to severely  
309 reduced left ventricle ejection fraction (98).

310 The pathophysiological mechanisms of how cardiac hypertrophy increases the risk of SCD are  
311 likely multifactorial, but ischemia and myocardial fibrosis are probably the most important.

312 Ischemia due to cardiac hypertrophy may arise from insufficient compensatory coronary artery  
313 growth and failure of coronary artery dilatation due to increased ventricle tension and stiffness  
314 (99). Cardiac hypertrophy is also often associated with myocardial fibrosis (100, 101), which  
315 increases the distance between adjacent myocytes and disturbs physiological electrical  
316 propagation, eventually leading to anatomic reentry (102). A recent study demonstrated that  
317 among CAD patients, myocardial fibrosis in cardiac magnetic resonance imaging was more  
318 strongly associated with SCD than left ventricle ejection fraction (103).

### 319 ***Fatty Heart***

320 The concept of the fatty heart has been described in the medical literature for at least 200 years  
321 (104, 105) and it was vigorously debated. Recognition of the global obesity epidemic at the end  
322 of the 20<sup>th</sup> century focused significantly on the possible existence of obesity-related  
323 cardiomyopathy (106).

324 In the early 2000s, Zhou et al demonstrated that obese rats developed lipid droplets in the  
325 myocardium and that cardiac dysfunction in such rats was caused by cardiac lipoapoptosis (107)  
326 (Figure 7). Subsequently, intramyocardial lipid accumulation was found in non-ischemic human  
327 heart failure, with the highest tissue levels among patients with diabetes and obesity (108). The  
328 development of “lipotoxic cardiomyopathy” is thought to occur due to a mismatch between  
329 cardiomyocyte fatty acid intake and oxidation. Fatty acids are a key source of energy for  
330 cardiomyocytes, and increased levels of circulating free fatty acids in obesity may lead to a  
331 disproportionally high level of fatty acid intake in the heart, which exceeds the mitochondrial  
332 oxidative capacity, and leads to organ dysfunction (106).

333 In addition to lipid accumulation in cardiomyocytes, prior studies have found that adipose tissue  
334 can accumulate in infarcted myocardium and co-localize with fibrosis (109, 110). Similarly to  
335 myocardial fibrosis, fat infiltration in the myocardium disturbs physiological electrical  
336 propagation and predisposes to ventricular arrhythmias (111). Given the co-localization with  
337 myocardial scars, one potential mechanism is fatty degeneration following MI. Fatty replacement  
338 of the myocardium is also a hallmark of arrhythmogenic right ventricular cardiomyopathy which  
339 is also associated with increased risk of SCD (112). However, the potential role of myocardial  
340 lipid accumulation and fatty replacement in the broader group of SCD victims is yet to be  
341 proven. Moreover, it is unclear whether the accumulation of intramyocardial fat after MI is  
342 related to obesity.

## 343 **Clinical Implications**

344 Sudden cardiac arrest is an extremely lethal event and leads to death within ten minutes if life-  
345 supporting interventions are not rapidly initiated. Although acute management of out-of-hospital  
346 cardiac arrests has improved in recent decades, long-term prediction and prevention remain the  
347 cornerstones of successful reduction of the premature SCD burden. Lifestyle intervention,  
348 weight-reducing diets, and exercise advice are likely to reduce premature all-cause mortality  
349 (113), and recent progress in obesity management (novel pharmacotherapies and bariatric  
350 surgery) has shown promising results in weight loss and reducing clinical risk factors.

### 351 *Clinical Benefits of GLP-1 Agonists and Bariatric Surgery*

352 In 2014, the FDA approved the first GLP-1 agonist to treat obesity, and since then, a growing  
353 body of evidence has demonstrated the cardiovascular benefits of GLP-1 agonists. In the STEP-1  
354 randomized trial, overweight and obese patients receiving GLP-1 agonist semaglutide achieved a  
355 mean body weight loss of 14.9%, which was significantly better in comparison to placebo (2.4%)  
356 and accompanied by a greater reduction in clinical risk factors (114). The effect of GLP-1  
357 agonists on cardiovascular outcomes was first tested in patients with diabetes, and several trials  
358 have demonstrated significant reductions in cardiovascular death(~13%), non-fatal MI(~9%),  
359 and HF hospitalization (~9%) (115). Beneficial effects on obesity lead to a hypothesis that GLP-  
360 1 agonists may reduce outcomes in nondiabetic obese patients as well. Recently published  
361 SELECT trial found that GLP-1 agonist semaglutide reduces major cardiovascular events (death  
362 from cardiovascular causes, nonfatal MI, or nonfatal stroke) also in nondiabetic obese patients  
363 with pre-existing cardiovascular disease by ~20% (116).

364 GLP-1 agonists' effect on weight reduction is mediated via the stimulation of satiety and  
365 reducing food intake(117), and a recent meta-analysis demonstrated that GLP-1 treatment leads  
366 to a decrease in both visceral and subcutaneous adipose tissue, and visceral adipose tissue  
367 reduction may be even greater than subcutaneous adipose tissue reduction (118). GLP-1  
368 receptors are also expressed in the heart and blood vessels, and may hence also have direct  
369 effects on the cardiovascular system irrespectively from weight reduction(117). There is yet no  
370 robust evidence on the effect of weight loss or GLP-1 agonists on SCD risk, but recent  
371 improvements are promising and future investigations are needed to examine whether GLP-1  
372 agonists have the potential to reduce the burden of premature SCD in obese patients.

373 Surgical interventions for obesity have been reported since the second half of the 20th century.  
374 After the first laparoscopic gastric bypass was performed in 1994, bariatric surgery started a  
375 rapid growth (119). Bariatric surgery is associated with greater weight reduction in comparison  
376 to pharmacological therapy (20-30%), but the risks of surgery remain higher (114, 120). Bariatric  
377 surgery has also been shown to associate with reduced cardiovascular risk factors and lower  
378 premature cardiovascular mortality (120, 121), but the effect on SCD risk has not been reported.

### 379 ***SCD Risk Stratification and Prevention in Obesity***

380 Long-term prediction and prevention of SCD are currently based on the assessment of left  
381 ventricle EF and the implantation of ICD for high-risk patients (122). While the primary  
382 prevention ICD remains important, the approach to risk stratification needs to be revisited. Of  
383 note, advances in HF management have led to an approximately 44% decline in the rate of SCD  
384 in HF (123) with a concomitant reduction in ICD therapy events (124, 125). Accurate SCD risk  
385 stratification in obesity is likely to require a combination of various biomarkers, including e.g.,  
386 metabolic alterations, omics data, cardiovascular imaging, and ECG, as well as more

387 sophisticated measurements of body composition and fat distribution than anthropometric  
388 measures (e.g., dual-energy X-ray absorptiometry, DXA).

389 Reducing the burden of SCD in obesity will require a comprehensive approach. Obesity is a  
390 result of a chronic mismatch between energy intake and consumption, and the underlying reasons  
391 for high energy intake are multifactorial including behavioral, genetic, and environmental  
392 determinants. The rapid increase in obesity in the last decades is not explainable by genetic or  
393 physiological changes, and according to previous studies, the most important causes for the  
394 increase in obesity are due to environmental changes that enable high energy intake (e.g., large  
395 portion sizes, the high energy density of the foods) (126, 127). Although weight loss and  
396 bariatric surgery lead to clinical benefits in various cardiovascular diseases(128), clinical  
397 guidance and the development of the healthcare system alone are likely not enough to curb the  
398 obesity epidemic, and more extensive consideration at the broader societal as well as health-  
399 policy levels will also be required (129).

#### 400 **Knowledge Gaps and Future Directions**

401 Published studies have demonstrated that increased BMI and especially visceral obesity carry an  
402 increased risk of SCD. While available literature provides valuable insights into obesity-related  
403 SCD, several knowledge gaps remain (Central Illustration).

404 Current evidence suggests that the increased SCD risk in obesity is not fully explainable by  
405 traditional cardiovascular risk factors and accelerated development of CAD/MI. All mediators  
406 for SCD risk in obesity are not fully understood, and other potential mediators include e.g.  
407 elevated free fatty acids (130, 131, 132), genetics (133), and obesity cardiomyopathy.

408 Intramyocardial fat can be detected with contrast-enhanced CT (134, 135), and prior studies have

409 shown that accumulation of fat in the myocardium leads to conduction disturbances and may  
410 predispose to VAs (111). However, prior studies have focused on post-MI patients, and it  
411 remains unclear whether intramyocardial fat is related to SCD in obese patients without CAD, or  
412 whether obesity is related to the amount of intramyocardial fat. A better understanding of SCD  
413 mediators in obesity is crucial in improving long-term prediction and prevention as well as  
414 identifying potential therapeutic targets, and further research is needed to investigate potential  
415 SCD mechanisms beyond CAD and traditional risk factors.

416 The traditional definition of obesity is based on the measurement of BMI, but the evidence  
417 suggests that the measures of visceral obesity are better predictors of morbidity and mortality  
418 (12). Indicators that are more precise than BMI warrant further investigation to enhance the  
419 identification and prevention of cardiovascular disease risk. Emerging metrics, such as body fat  
420 distribution or body composition may provide a more accurate assessment of obesity than  
421 traditional anthropometric measures and should be assessed in future studies.

422 Further efforts are also needed to investigate the effect of novel obesity therapies on SCD risk.  
423 The SELECT trial demonstrated that GLP-1 agonists reduce the risk of major cardiovascular  
424 events, but the effect on SCD is unclear. GLP-1 agonists have been associated with increased  
425 resting heart rate (a risk factor for SCD), which has raised some safety concerns regarding the  
426 risk of ventricular arrhythmias (136). In patients with type 2 diabetes, GLP-1 agonists have not  
427 been shown to increase or decrease the risk of VAs or SCD (137, 138), but the effects in patients  
428 with obesity need detailed investigation. With the current medical therapy, the event rate of SCD  
429 can be substantially low, which challenges the detection of statistically and clinically meaningful  
430 effects. This would require a large sample size and a careful selection of patients with obesity  
431 and a high risk of SCD. The development of an accurate SCD risk stratification in obesity may

432 be a prerequisite for studying the effectiveness of GLP-1 agonists in reducing the risk of obesity-  
433 related SCD.

434 Current guidelines recommend preventive ICD therapy only for those with EF<35% (primary  
435 prevention) or a history of a life-threatening arrhythmia (secondary prevention) (122). The major  
436 limitation of the current approach is low sensitivity, since at least 70% of SCD cases occur in  
437 subjects that are not classified as high-risk patients and do not fulfill the current criteria for ICD  
438 implantation (139). Approximately 40-50% of SCDs may even be the first manifestation of the  
439 underlying cardiac disease(1), and low-cost high-throughput screening tools, especially ECG,  
440 have attained interest in the research field. Accumulation of ECG abnormalities into electrical  
441 risk scores has been shown to have a relatively good ability to identify patients at high risk of  
442 SCD(81, 82), and ECG abnormalities can also improve risk prediction when added to clinical  
443 risk markers (140). The usefulness of ECG risk scores may however be affected by body fat (24),  
444 and the development of body fat-adjusted ECG risk scores is probably warranted to improve  
445 ECG-based screening methods in obese patients. Most recently, an artificial intelligence  
446 algorithm that can predict SCD risk from the entire waveform instead of individual ECG risk  
447 markers has been made available.(141)

448 The development of SCD is generally thought to require a combination of an underlying cardiac  
449 substrate with one or more triggers. While obesity-related cardiac hypertrophy and CAD can  
450 create a substrate for SCD, obstructive sleep apnea may act as a potential trigger for life-  
451 threatening arrhythmias. Epidemiological evidence supports the role of obstructive sleep apnea  
452 as an SCD precipitator (73, 74, 79), but previous randomized trials of CPAP for secondary  
453 cardiovascular prevention in obstructive sleep apnea have reported neutral findings(142, 143,  
454 144). However, these randomized trials have been criticized due to the exclusion of high-risk

455 patients and low adherence to CPAP therapy, and the effect of CPAP therapy on reducing SCD  
456 risk in obese patients remains inconclusive.

457 The association between obesity and SCA presentation with higher rates of non-shockable  
458 rhythms could result in worse survival outcomes and needs further investigation. For example,  
459 are the higher rates of PEA and asystole in obese individuals directly related to the “obesity  
460 substrate” or confounded by features related to SCA circumstances or resuscitation-related  
461 factors in obese individuals? If SCA survival is lower in obese individuals, how could outcomes  
462 be improved?

463 The impact of obesity on SCD across socioeconomic status and racial/ethnic groups needs  
464 further investigation. There are significant differences in the prevalence of obesity with regard to  
465 race/ethnicity and social determinants. For example, obesity is more common among some U.S.  
466 racial/ethnic minorities, such as African Americans and Hispanic, as well as in lower  
467 socioeconomic groups, but the prevalence is lower in Asian Americans (145, 146). Consistently,  
468 the risk of SCD is higher among African Americans and in lower socioeconomic groups (3, 147),  
469 but it is unclear to what extent this is explained by the higher rates of obesity. Obesity may hence  
470 have a higher impact on the overall SCD burden in some communities, and a recent multiethnic  
471 community-based study from the U.S. found that while the SCD rate was similar in Hispanic and  
472 White individuals, obesity and lower socioeconomic status were more common SCD  
473 characteristics among Hispanic (148). Socioeconomic disadvantages and variable access to  
474 preventive healthcare may have an important effect on the risk of obesity and SCD, and  
475 community-specific areas of focus for education and preventive healthcare may have the  
476 potential to improve early diagnosis and SCD prevention. More work is needed to investigate the  
477 burden and characteristics of obesity-related SCD across diverse communities.

478

479

480 **Bullet points**

- 481 • Most of the obesity-related premature deaths are due to cardiovascular diseases
- 482 • Visceral obesity is a stronger risk factor for sudden cardiac death (SCD) than BMI
- 483 • Obesity-associated SCD is often characterized by non-ischemic cardiac hypertrophy or
- 484 coronary artery disease
- 485 • Community-level strategies, weight loss therapies, and SCD risk stratification specific to
- 486 obesity warrant further investigative focus and have the potential to reduce the burden of
- 487 obesity-related SCD

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869

870 **Figure titles**

871 **Central Illustration.** Sudden cardiac death (SCD) in obesity: potential mechanisms and future  
872 directions for management. Especially visceral obesity increases the risk of SCD, and the risk is  
873 likely mediated by several alterations in the cardiovascular system due to obesity. Future studies  
874 are required to investigate novel individual and community-based methods to decrease the  
875 burden of obesity-related SCD.

876 **Figure 1.** Global BMI-related mortality and disability-adjusted life-years 1990-2015. The figure  
877 shows the number of deaths and disability-adjusted life-years in adults that are related to a high  
878 BMI in 1990 and 2015 according to the BMI level and cause. Panel A: BMI-related disability-  
879 adjusted life-years in 1990. Panel B: BMI-related disability-adjusted life-years in 2015. Panel C:  
880 BMI-related mortality in 1990. Panel D: BMI-related mortality in 2015. BMI threshold for  
881 overweight (25-29 kg/m<sup>2</sup>) and obesity (>30 kg/m<sup>2</sup>) are marked with the vertical lines. From:  
882 GBD 2015 Obesity Collaborators; Afshin A, et al. *N Engl J Med.* 2017;377:13-27.

883 **Figure 2.** The relationship between sagittal abdominal diameter, sudden death, and fatal MI.  
884 Data from the Paris Prospective study showed that abdominal obesity increases the risk of SCD  
885 regardless of BMI, and the association was stronger between abdominal obesity and SCD than  
886 between abdominal obesity and fatal MI. From: Empana P, et al. *Circulation.* 2004;110:2781-5.

887 **Figure 3.** Potential development of obesity cardiomyopathy. Obesity leads to significant  
888 hemodynamic changes (e.g., higher blood volume) which promote cardiac hypertrophy,  
889 dilatation, and heart failure. From: Lavie CJ, et al. *J Am Coll Cardiol.* 2018;72:1506-1531.

890 **Figure 4.** Obesity and cardiomegaly. A study from the U.K. reported autopsy findings in sudden  
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892 obesity and normal weight controls. Cases with OCM presented with left ventricle enlargement  
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894 **Figure 5.** Epicardial adipose tissue and ventricular arrhythmias. Panel A illustrates the  
895 infiltration of adipose tissue in the myocardium and a zigzag electrical activation pattern leading  
896 to re-entry. Panel B illustrates how regional conduction disturbances lengthen the distance and  
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901 **Figure 6.** Obstructive sleep apnea (OSA) and diurnal variation of sudden death. A study on  
902 polysomnograms and the death certificates of 112 sudden cardiac death (SCD) victims found that  
903 cases with OSA had a peak in SCD occurrence during sleeping hours. From: Gami AS, et al. N  
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905 **Figure 7.** Intramyocardial lipid accumulation. Lipid droplets in myocardium sections of an  
906 untreated obese Zucker Diabetic Fatty (ZDF) rat (left) and a troglitazone-treated obese ZDF rat  
907 (right). Lipid droplets appear in white and are marked with an I. From: Zhou YT, et al. Proc Natl  
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