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Original Research

Obesity in young sudden cardiac death: Rates, clinical features, and insights into people with body mass index >50kg/m^2

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ABSTRACT

Objective: To contextualize obesity rates in young sudden cardiac death (SCD) against the age-matched national population, and identify clinical and pathologic features in WHO class II and III obesity.
Methods: A prospective state-wide out-of-hospital cardiac arrest registry included all SCDs in Victoria, Australia from 2019–2021. Body mass indices (BMIs) of patients 18-50 years were compared to age-referenced general population. Characteristics of SCD patients with WHO Class II obesity (BMI ≥30kg/m^2) and non-obesity (BMI<30kg/m^2) were compared. Clinical characteristics of people with BMI>50kg/m^2 were assessed.
Results: 504 patients were included. Obesity was strongly over-represented in young SCD compared to the age-matched general population (55.0% vs 28.7%, p<0.0001). Obese SCD patients more frequently had hypertension, diabetes and obstructive sleep apnoea (p<0.0001, p=0.009 and p=0.001 respectively), ventricular fibrillation as their arrest rhythm (p=0.008) and left ventricular hypertrophy (LVH) (p<0.0001). Obese patients were less likely to have toxicology positive for illicit substances (22.0% vs 32.6%, p=0.008) or history of alcohol abuse (18.8% vs 26.9%, p=0.030). Patients with BMI>50 kg/m^2 represented 8.5% of young SCD. LVH (n=26, 60.5%) was their predominant cause of death and only 10 (9.3%) patients died from coronary disease.
Conclusion: Over half of young Australian SCD patients are obese, with all obesity classes over-represented compared to the general population. Obese patients had more cardiac risk factors. Almost two thirds of patients with BMI>50 kg/m^2 died from LVH, with fewer than 10% dying from coronary disease.

Abbreviations: BMI, body mass index; EndUCD, End Unexplained Cardiac Death Registry; OHCA, out of hospital cardiac arrest; SCD, sudden cardiac death; VIFM, Victorian Institute of Forensic Medicine.

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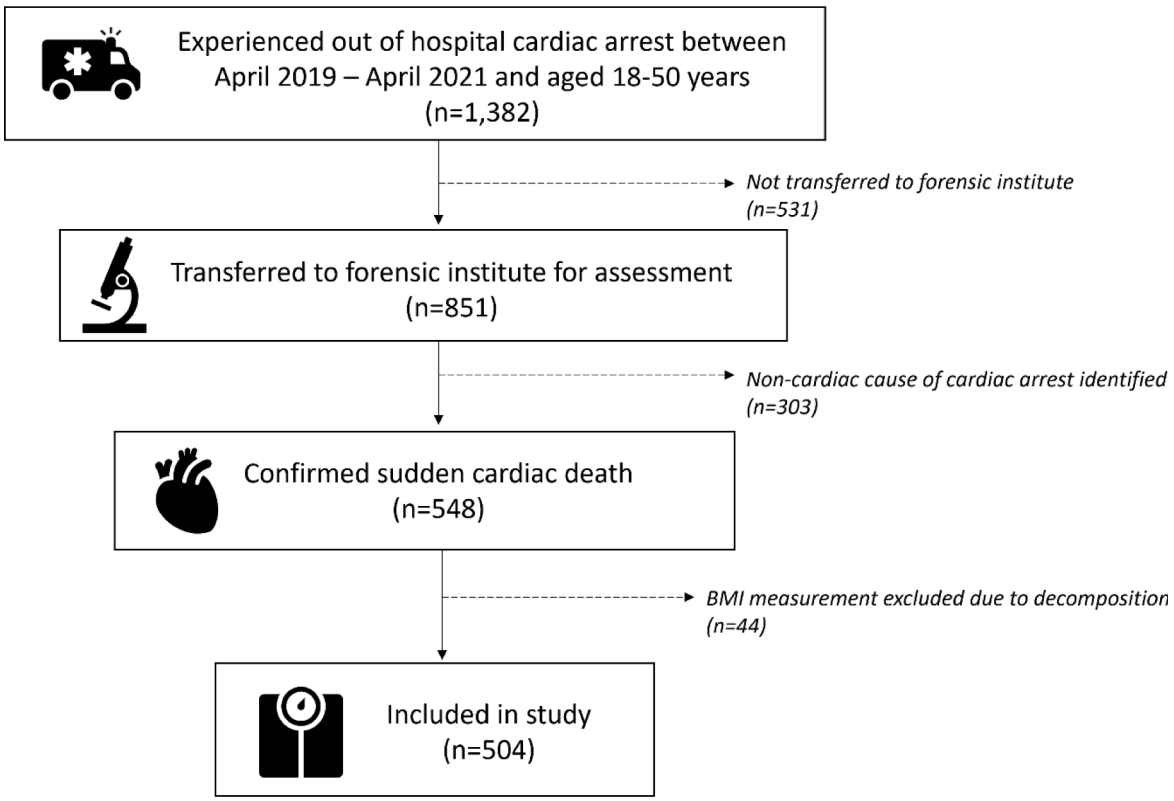

Fig. 1. CONSORT diagram indicating case inclusion criteria.

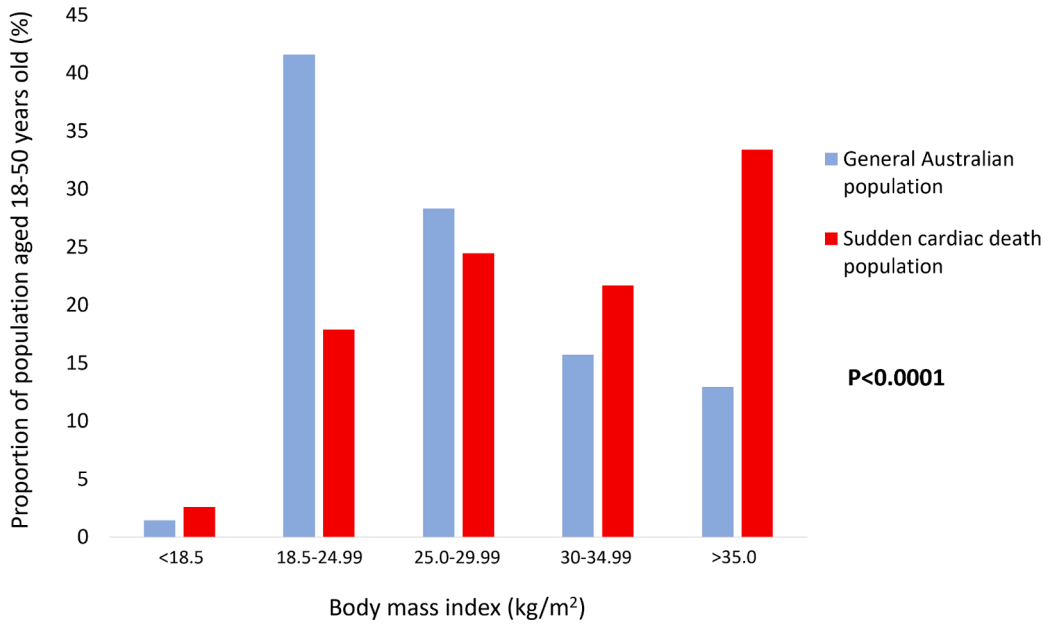

Fig. 2. Body mass index data of young SCD patients (red) contextualised against the general Australian population of the same age (blue).

1. Introduction

Obesity is a global health problem with major cardiovascular complications and impact on health systems. Both the absolute number and the degree of obesity severity are increasing worldwide [1]. Obesity has been linked with sudden cardiac death (SCD) in a dose-response manner [2,3], with reported increased rates of cardiomyopathy, arrhythmia, and coronary artery disease. Overall, obesity is now considered the commonest non-ischemic cause of SCD [4].

Forensic facilities, who provide the majority of investigations for young SCD patients, have documented increasing rates of obesity in their patient cohort with a more than three-fold increase in the number of obese patients and almost two-fold increase in morbidly obese patients received [5]. It is not clear whether this reflects general population trends, or whether obese patients are truly over-represented in sudden death cohorts. Previous studies utilising SCD populations have suggested that the rate of obesity in SCD approximates the rate of obesity in the general population [6]. Clarifying whether obesity is more

Table 1
Clinical and pathological characteristics of obese and non-obese individuals deceased from SCD.

	Obese (BMI≥30kg/m^2)	Non-obese (BMI<30kg/m^2)	Significance
Clinical characteristics			
Number	277	227	
Male gender (%)	201 (72.6%)	177 (78.0%)	P=0.163
Age (years)	43.13 [35.8 – 47.9]	42.9 [34.9-47.4]	P=0.5698
Known to a cardiologist pre-SCD (%)	62 (22.4%)	43 (18.9%)	P=0.596
Hypertension (%)	59 (21.3%)	21 (9.3%)	**P<0.0001**
Dyslipidaemia (%)	37 (13.4%)	18 (7.9%)	P=0.052
Diabetes (%)	40 (14.4%)	16 (7.0%)	**P=0.009**
Smoker (current or former) (%)	76 (27.4%)	54 (23.8%)	P=0.352
History of alcohol abuse (%)	52 (18.8%)	61 (26.9%)	**P=0.030**
Psychiatric illness (%)	83 (30.0%)	65 (28.6%)	P=0.744
Obstructive sleep apnoea (%)	28 (10.1%)	6 (2.6%)	**P=0.001**
Prior stroke (%)	2 (0.7%)	6 (2.6%)	P=0.086
Antiplatelet use (%)	11 (4.0%)	5 (2.2%)	P=0.260
Beta-blocker use (%)	23 (8.3%)	14 (6.2%)	P=0.360
ACE inhibitor / ARB / ARNI use (%)	25 (9.0%)	8 (3.5%)	**P=0.013**
Statin use	22 (7.9%)	6 (2.6%)	**P=0.010**
Cardiac arrest details			
Circumstances of arrest (%)	Sleeping 114 (41.1%) Sedentary 144 (52.0%) Exercise 19 (6.9%)	Sleeping 83 (36.6%) Sedentary 125 (55.1%) Exercise 19 (8.3%)	P=0.529
Witnessed arrest (%)	62 (22.4%)	45 (19.8%)	P=0.485
Bystander CPR[a] (%)	45 (72.6%)	29 (64.4%)	P=0.368
Arrest rhythm (%)	VF 54 (19.5%) VT 2 (0.7%) PEA 14 (5.1%) Asystole 207 (74.7%)	VF 22 (9.7%) VT 0 (0.0%) PEA 17 (7.5%) Asystole 188 (82.8%)	**P=0.008**
Defibrillation[b] (%)	55 (98.2%)	21 (95.5%)	P=0.488
Transported to hospital (%)	28 (10.1%)	14 (6.2%)	P=0.111
Forensic results			
Autopsy performed (%)	243 (87.7%)	190 (83.7%)	P=0.196
Median heart weight (g)	539 [450 – 638]	427.5 [348-490]	**P<0.0001**
LVH[c] (%)	167 (68.7%)	59 (31.1%)	**P<0.0001**
Toxicology positive for illicit substances (%)	61 (22.0%)	74 (32.6%)	**P=0.008**
Cause of SCD (%)	Coronary 100 (36.1%) Unascertained 72 (26.0%) LVH 85 (30.7%) Other 20 (7.2%)	Coronary 85 (37.4%) Unascertained 98 (43.2%) LVH 29 (12.8%) Other 15 (6.6%)	**P<0.0001**

a = bystander CPR presented as a proportion of witnessed arrests; b = defibrillation presented as a proportion of arrests with a rhythm of VT/VF; c = cardiomegaly reported as a proportion of cases that underwent autopsy
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; LVH = left ventricular hypertrophy; PEA = pulseless electrical activity; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia
Categorical values are represented as absolute value (%) while continuous values are represented as median [inter-quartile range].

common in young SCD patients than the general population would be an important insight into a potentially modifiable SCD risk factor.

Insights into the most obese patients have been small to date. Several studies have reported upon findings in cohorts of obese or morbidly obese patients; none have reported upon findings in populations with a body mass index (BMI) exclusively greater than 50kg/m^2. Given the reports of BMI and SCD interacting in a dose-response manner and increasing severity of obesity globally, examining the clinical and pathologic findings in a cohort of patients with a BMI>50 kg/m^2 would be informative.

We therefore utilised a prospective state-wide out of hospital cardiac arrest (OHCA) registry to investigate the relationship between obesity and young SCD. The aims of this study were to (a) determine whether BMI profiles in a young SCD population differed from age-referenced general population values, (b) define what differentiated obese SCD and non-obese SCD patients, and (c) to provide an in-depth profile of clinical and pathologic features of SCD in the those with a BMI>50kg/m^2.

2. Methods

2.1. Data sources

EndUCD registry: The End Unexplained Cardiac Death (EndUCD) Registry is a prospective state-wide registry in Victoria, Australia (population 6.5 million). It collates data from ambulance, hospital and forensic services to provide an adjudicated cardiac arrest data source on all OHCAs occurring in Victorians aged 1–50 years old [7].

General Australian population: Data regarding BMIs of the general Australian population aged 18–50 years old was obtained from the Australian Bureau of Statistics' National Health Survey [8]. The National Health Survey was conducted as a nationwide study from 2017 to 2018, sampling 21,300 Australians in terms of anthropometric measurements and general health. BMI data was obtained as proportions in BMI categories of <18.5kg/m^2, 18.5–24.99kg/m^2, 25–29.99kg/m^2, 30–34.99kg/m^2 and >35.0kg/m^2 within the age range of 18–50 years old.

2.2. Patient population and assessment

Inclusion criteria: This study included Victorians aged 18–50 years old who experienced an SCD during the period April 2019–April 2021 (Fig. 1) and were transferred to the Victorian Institute of Forensic Medicine (VIFM) for examination (either comprehensive autopsy or external examination only provided a BMI was calculated and reported).

Exclusion criteria: Patients were not included in the study if they survived their cardiac arrest or died but were not transferred to the VIFM. Patients were also excluded from the study if forensic investigations revealed a non-cardiac cause of their out-of-hospital cardiac arrest (for example, a pulmonary embolus) or if they were severely decomposed at the time of forensic assessment, rendering their anthropometric measurements unreliable.

Patients who underwent autopsy for the investigation of SCD had a detailed assessment of the cardiac system undertaken according to minimum standards criteria at VIFM. This included a comprehensive description of cardiac anatomy, as well as histopathology. Cardiac size was recorded both as an exact mass (in grams), and left ventricular wall measurements taken. Left ventricular hypertrophy has been defined for this paper as the presence of left ventricular wall diameter >15mm in the presence of a heart weight of 500g in males or 400g in females [6]. Toxicology was performed when clinically indicated.

Cardiac findings were collapsed into primary categories of unascertained cause, left ventricular hypertrophy (LVH), coronary disease and all other cardiac causes (Supplementary Table 1). Unascertained cause was defined as no cause being found after extensive investigations including autopsy and post-mortem genetic testing. 'All other cardiac causes' included all other cardiac causes such as myocarditis, valvular disease, pulmonary hypertension or aortic dissection.

2.3. Methodology

Comparison of study participants to the general Australian population:

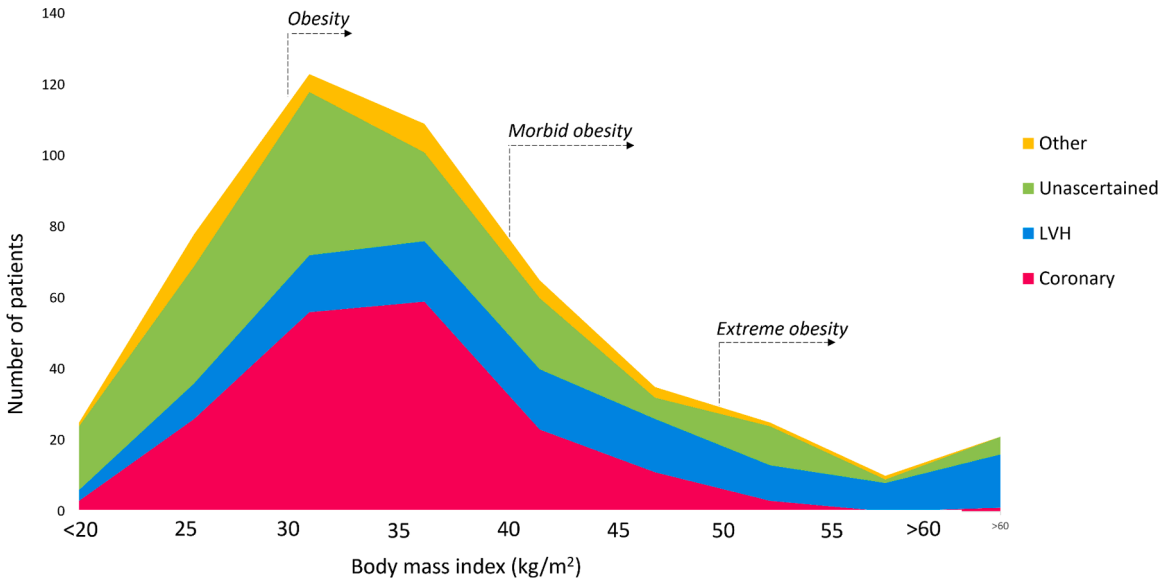

Fig. 3. Causes of death according to body mass index

Study participants were compared to the age-matched general Australian population using the same data ranges as provided by the National Health Survey [8].

Comparison of obese and non-obese study participants: Clinical, arrest-related and forensic details of all SCD patients were compared according to whether they were obese (BMI≥30kg/m^2) or non-obese (BMI<30kg/m^2).

Patients with BMI>50kg/m^2: Terminology regarding obesity can be heterogenous. BMI>50kg/m^2 can be variously described as class III obesity, class IV obesity, extreme obesity or super obesity. In this study, we utilised the recommended description of 'extreme obesity' or 'WHO class III obesity with BMI>50kg/m^2,' for patients with a BMI of >50kg/m^2 [9]. Descriptive data of patients with BMI>50kg/m^2 and their cause of death and medical history was compiled.

Statistical analysis: For continuous variables, normality was assessed using a Shapiro-Wilk test and then a Mann-Whitney U test used to compare non-parametric variables (results presented as medians with interquartile ranges) or a paired t-test used to compare normally distributed variables (results presented as means with standard deviations). A chi-squared test was used to compare categorical variables, with results expressed in absolute values and proportions. If cell count was anticipated to be less than fifteen, Fisher's exact test was used. A P value of <0.05 was used as the threshold of significance. All statistical analyses were performed in STATA v14.0 (STATACorp, Texas, USA).

Ethics: The EndUCD registry holds over-arching ethical approval from the Alfred Hospital, Hospital Research Ethics Committee (HREC Approval 597/18).

3. Results

3.1. Overall results and indexing against age-standardised general Australian population

504 individuals deceased from SCD were included in the study. BMIs ranged from 12.8kg/m^2 to 117.8kg/m^2, with median BMI 30.9kg/m^2 (IQR 25.9-37.7kg/m^2).

A highly significant difference was evident between the BMIs of the SCD cohort and the general Australian population (Fig. 2). Obesity was significantly more common in the SCD cohort compared to the general Australian population (55.0% vs 28.7%, p<0.0001), with all classes of obesity more common in the SCD cohort.

3.2. Obese versus non-obese persons experiencing SCD

The overall prevalence of obesity (BMI>30kg/m2) was 55.0% (n=277). Obese individuals were more likely to have hypertension (21.3% vs 9.3%, p<0.0001), diabetes (14.4% vs 7.0%, p=0.009) and obstructive sleep apnoea (10.1% vs 2.6%, p=0.001) as comorbidities (Table 1). They were less likely than non-obese individuals to have a history of alcohol abuse (18.8% vs 26.9%, p=0.030). They were more likely to be prescribed angiotensin converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor neprilysin inhibitors (9.0% vs 3.5%, p=0.013) and more likely to be prescribed statin therapy (7.9% vs 2.6%, p=0.01).

Regarding their cardiac arrest, no differences were observed between obese and non-obese patients with regards to the circumstances of the arrest, the likelihood of the arrest being witnessed or of receiving bystander cardiopulmonary resuscitation. Obese patients were more likely to have ventricular fibrillation as their arrest rhythm (19.5 vs 9.7%, p=0.008) but there were no differences in rates of defibrillation of eligible patients.

On forensic assessment, significant differences were observed between obese and non-obese patients. Obese patients were less likely to have toxicology positive for illicit substances (22.0% vs 32.6%, p=0.008). They had generally larger hearts, both in terms of absolute mass (median 539 vs 427.5g, p<0.0001) and rates of LVH (68.7% vs 31.1%, p<0.0001). LVH was more commonly identified at autopsy (p<0.0001) as BMI increased (Fig. 3).

3.3. Persons with BMI >50kg/m^2 and SCD

Forty-three individuals (8.5%) were identified to have a BMI of >50kg/m^2. Within this group, there was a high burden of cardiovascular risk factors including hypertension, diabetes and obstructive sleep apnoea although few (n=8, 18.6%) had been reviewed by a cardiologist prior to their SCD (Table 2).

Patients with a BMI of >50kg/m^2 were very unlikely to have a witnessed arrest (2.3% witnessed) and consequently the majority (n=40, 93.0%) were discovered in asystole. Few patients met defibrillation criteria (n=1, 2.3%) and few were transported to hospital (n=2, 4.7%), with 38 being declared dead at the scene.

The pathologic features noted in obese patients were further augmented in patients with a BMI of >50kg/m^2, with very large heart weights (median weight 683g, IQR 596-828g) and very high rates of

Table 2
Characteristics of patients with super obesity (BMI>50kg/m^2).

Clinical characteristics	
Number	43
Median BMI (kg/m^2)	58.8 [54.3-66.3]
Male gender (%)	23 (53.5%)
Median age (years)	42.6 [37.7-48.0]
Known to a cardiologist pre-SCD (%)	8 (18.6%)
Hypertension (%)	14 (32.6%)
Dyslipidemia (%)	4 (9.3%)
Diabetes mellitus (%)	9 (20.9%)
Smoker (current or former) (%)	13 (30.2%)
History of alcohol abuse (%)	7 (16.3%)
Psychiatric illness (%)	12 (27.9%)
Obstructive sleep apnoea (%)	14 (32.6%)
Prior stroke (%)	1 (2.3%)
Cardiac arrest-related details	
Circumstances of arrest	Sleeping 23 (53.5%) Sedentary 19 (44.2%) Exercise 1 (2.3%)
Witnessed arrest (%)	1 (2.3%)
Bystander CPR[a] (%)	0 (0.0%)
Arrest rhythm	Asystole 40 (93.0%) PEA 2 (4.7%) VF 1 (2.3%)
Defibrillation[b] (%)	1 (100%)
Transported to hospital (%)	2 (4.7%)
Forensic results - overall	
Autopsy performed (%)	36 (83.7%)
Median heart weight (g)	683 [596-828]
LVH[c]	35 (97.2%)
Toxicology positive for illicit substances (%)	6 (14.0%)
Cause of death	LVH 26 (60.5%) Unascertained 10 (23.3%) Coronary 4 (9.3%) Other 3 (7.0%)
Forensic results – histopathology	
Myocyte hypertrophy	20 (76.9%)
Any fibrosis[d]	18 (69.2%)
Conduction system infiltration by fibrosis / fat	1 (3.8%)
Interstitial fibrosis	13 (50.0%)
Perivascular fibrosis	11 (42.3%)
Fatty infiltration in myocardium	5 (19.2%)

a = bystander CPR presented as a proportion of witnessed arrests; b = defibrillation presented as a proportion of arrests with a rhythm of VT/VF; c = LVH reported as a proportion of cases that underwent autopsy; d = proportion of SCDs with LVH
BMI = body mass index; LVH = left ventricular hypertrophy; PEA = pulseless electrical activity; SCD = sudden cardiac death; VF = ventricular fibrillation; Categorical values are represented as absolute value (%) while continuous values are represented as median [inter-quartile range].

Supplementary Table 1
Definitions used to adjudicate cause of death.

Term	Macroscopic features
Coronary disease	Atherosclerosis with estimated luminal narrowing >75% or described visually as 'severe'
Unascertained cause of death	Morphologically normal heart or no probable cause of death found on investigations
Left ventricular hypertrophy (LVH)	Left ventricular wall thickness >15mm and heart weight >500g in males or >400g in females
Other cardiac causes	All other cardiac causes of sudden death

LVH (n=35, 97.2% of autopsies). Only 10 patients (9.3%) had an SCD due to coronary disease (Fig. 4).

Histopathological analysis of the patients with a BMI of >50kg/m^2 who had LVH demonstrated high rates of myocyte hypertrophy (n=20, 76.9%) and fibrosis (n=18, 69.2%). Five patients (19.2%) had fatty infiltration in their myocardium, with one patient having fatty infiltration of their atrioventricular node of uncertain clinical significance.

4. Discussion

This study identified a 55% rate of obesity in young adult SCD, which is much higher than previously reported internationally and approximately two-fold higher than obesity rates in the age-matched general Australian population. Obese SCD patients exhibited a heavier burden of cardiovascular risk factors. Individuals with a BMI of >50kg/m^2 comprised 8.5% of young SCD, with adverse resuscitation profiles and LVH identified at post-mortem examination.

4.1. Contextualising obesity in SCD against population obesity rates

Our study provides novel information in several areas. Our finding that 55% of young SCD patients were obese is far in excess of rates in other young SCD registries – for example, that of Finocchiaro et al. who reported a 20% prevalence of obesity in a United Kingdom cohort or Wisten et al. who reported a 15% prevalence in their Swedish cohort [6,10]. Intriguingly, despite using a similar methodology to our study, Finocchiaro et al. reported a much more population-concordant rate of obesity in SCD (20% obesity rate in SCD, 20% obesity rate in age-matched general population of United Kingdom). These differences are surprising given the high population rates of obesity in both the United Kingdom and Australia, and would be valuable to examine in future studies.

Excess mortality due to SCD in obesity has previously been demonstrated, consistent with our findings. The annual SCD rate in morbidly obese people has previously been stated to be 12-40 times the SCD rate in matched non-obese populations [11,12]. In a population of over 10,000 middle-aged subjects followed over forty years, obese patients had an almost 80% increased risk of SCD compared to normal-weight subjects [13]. Aune et al. concluded from a meta-analysis of eleven publications including over 406,000 patients that the relationship between obesity and SCD is a dose-response one, with a 16% increase in the relative risk of SCD for each five unit increase in BMI [2]. Our study confirms these findings utilizing a cohort of patients who have had the outcome of definite SCD, with individual adjudication of each case to confirm cardiac causation.

4.2. Insights into obese patients and patients with BMI>50kg/m^2 experiencing SCD

The comparison of SCD in obese versus non-obese patients identified that obese patients exhibited more cardiovascular risk factors such as hypertension, diabetes mellitus and obstructive sleep apnoea. Although coronary disease was the commonest cause of death in both groups, it was surprisingly not more common in the obese patient cohort who had the heavier burden of cardiovascular risk factors. Our finding that coronary disease was the commonest overall cause of death differs from the findings of both Wisten et al. and Finocchiaro et al., who identified unascertained arrest as the commonest cause of SCD in the young. This difference is likely due to our study including patients up to 50 years whereas both other papers included patients aged under 35 years [6,10].

Our cohort of 43 patients with a BMI of >50kg/m^2 is the largest reported group of extremely obese patients experiencing SCD to date, with BMIs ranging up to almost 120kg/m^2. The 8.5% prevalence rate of BMI >50kg/m^2 in our young SCD cohort is also the highest-reported to date. With rates and severity of obesity increasing globally [5,14], it is timely to examine whether these patients comprise a particularly high-risk group for SCD. Of note, although the BMI>50kg/m^2 cohort exhibited high rates of cardiovascular risk factors, few had been reviewed by a cardiologist. Consistent with previous studies, rates of coronary disease were surprisingly low, at <10% [6,15].

Concerningly, almost all of these patients' cardiac arrests were unwitnessed, potentially reflecting limited household members or social support. This translated into low rates of shockable rhythms and limited bystander cardiopulmonary resuscitation and low rates of hospital

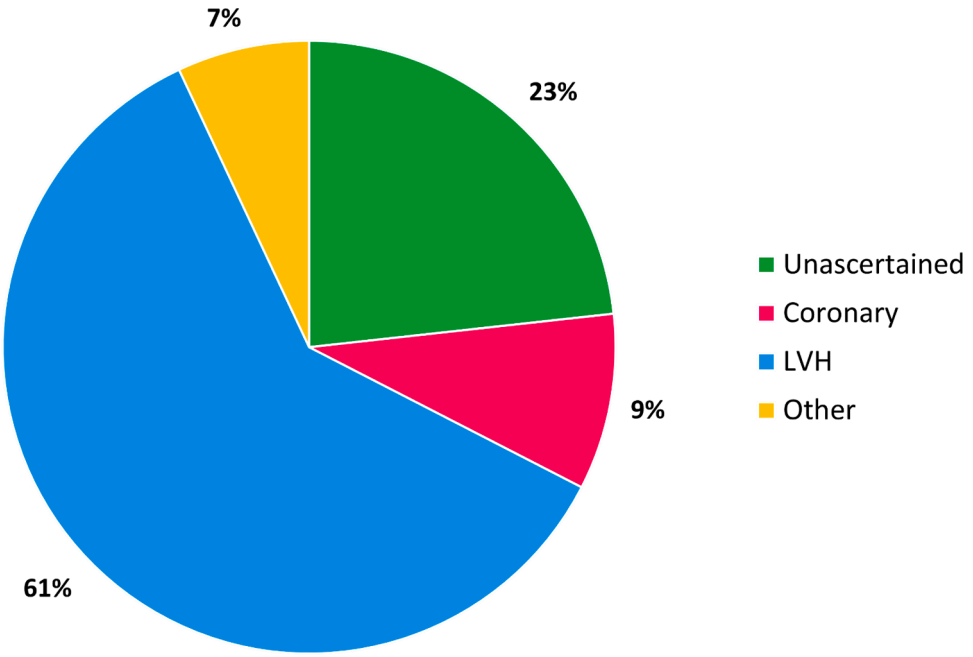

Fig. 4. Causes of death in patients with BMI>50kg/m^2.

transfer. These concerning trends may warrant further assessment and consideration of targeted strategies for a high-risk population. Previous studies in obese patients have already indicated higher thirty-day mortality in the subset of patients who are successfully resuscitated from their cardiac arrest and transported to hospital [16,17].

4.3. Mechanisms of death in LVH

In this study, LVH occurred more than twice as commonly in obese patients and was the dominant autopsy finding (60.5%) in patients with a BMI of >50kg/m^2. These findings are consistent with other international studies. Kortelainen et al. reported in their study of 235 morbidly obese patients that the most common cause of death observed was 'nonspecific cardiomyopathy', occurring in 28.9% of cases [14], while Duflou et al. identified LVH as the cause of death in over one-third of 28 morbidly obese patients [15].

The nature and role of LVH in SCD has been debated, as has the exact definition of LVH in obesity. LVH in the obese is believed to be a common cause of heart failure, caused by chronically increased afterload, generalised oxidative stress, systemic inflammation and potentially direct lipotoxicity inducing a dilated cardiomyopathy [18]. In living patients, data from the Framingham study indicated that each one-unit increase in BMI increased risk of heart failure by 5% for males, and that obesity was the sole cause of cardiac failure in 11% of males [19]. Increasing cardiac size is associated with increasing heterogeneity of ventricular repolarization, with electrocardiographic dispersion commonly reported [20,21]. This may correlate to an increased risk of arrhythmias [1] and consequently, LVH in the obese has been proposed as a frequent cause of SCD. In our study, ventricular fibrillation did occur more commonly in obese patients, but without pre-mortem electrocardiographic tracings it is not possible to comment on whether such reported electrical dispersion may have been present in our subjects.

On a histopathological level, findings in obesity-related LVH have been debated [22]. Myocardial hypertrophy and myocardial fibrosis have both been reported, creating a potential substrate for malignant arrhythmias [23,24]. Both however, may also be seen as a consequence of hypertension, creating a degree of confounding. Duflou et al. reported that the predominant mechanism of LVH in morbidly obese patients was that of myocyte hypertrophy without an increase in the distribution or amount of cardiac fibrosis [15]. In our cohort, we observed fibrosis in over two thirds of people with BMI >50kg/m^2 and LVH, which may have facilitated fibrosis-related arrhythmias. Infiltration of the conducting system has also been reported to be an important cause of SCD in the young [25]; however, we observed fatty infiltration of the cardiac conduction system in only one case.

4.4. Limitations

Data on distribution of obesity (ie central adiposity) and more specific anthropometric measurements such as waist and hip circumference were not available to investigators. Adabag et al. [26] have suggested that generalized obesity is associated with SCD via traditional cardiovascular risk factors whereas central obesity is independently associated with SCD by pathways independent of traditional cardiovascular risk factors. It would be of interest to correlate these more detailed anthropometric measurements to clinical and pathologic features of SCD.

5. Conclusion

Over half of young adult Australian SCD patients were obese, with over-representation of all classes of obesity compared to the general population. Obese patients were more likely to have traditional cardiac risk factors and have LVH at autopsy. Almost two thirds of patients with BMI of >50kg/m^2 died with LVH, with fewer than 10% dying due to coronary disease.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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