**Impact of demographic features, lifestyle and comorbidities on the clinical expression of hypertrophic cardiomyopathy**

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Keywords: Hypertrophic cardiomyopathy, natural history, environment

Word count: 3,693

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**Funding sources:** IO was supported by the Italian Ministry of Health (Left ventricular hypertrophy in aortic valve disease and hypertrophic cardiomyopathy: genetic basis, biophysical correlates and viral therapy models” (RF-2013-02356787), and NET-2011-02347173 (Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy); and by the ToRSADE project (FAS-Salute 2014, Regione Toscana). GF was supported by the charity Cardiac Risk in the Young (CRY) and the Wolfson Foundation. MP and SS are supported by CRY.

*Felix qui potuit rerum cognoscere causas*

Happy is he who has been able to learn the causes of things

[Virgil](https://it.wikipedia.org/wiki/Publio_Virgilio_Marone), [Georgiche](https://it.wikipedia.org/wiki/Georgiche" \o "Georgiche), II, 489

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disease defined clinically by the presence of unexplained left ventricular hypertrophy. In most patients HCM is caused by mutations in genes encoding proteins of the cardiac sarcomere1–4. Symptoms include dyspnoea on exertion, fatigue, angina, atypical chest pain, syncope, and palpitations. A significant proportion of patients are asymptomatic throughout life and the diagnosis often follows the incidental finding of an abnormal ECG or the detection of a cardiac murmur. The natural history is variable; many patients have a normal life expectancy whereas others may experience disease progression with profound exercise limitation, recurrent arrhythmias and premature death largely due to heart failure5,6. Sudden cardiac death (SCD) is relatively rare, occurs more commonly in young patients and is caused mainly by ventricular arrhythmias that can be effectively treated with an implantable cardioverter defibrillator (ICD)7,8.

HCM is a typical example of monogenic disease where a single nucleotide mutation is sufficient to cause a complex pathologic phenotype9. Genetic testing identifies pathogenic or likely pathogenic variants in 30 to 50% of HCM patients, and over 1.000 distinct mutations in genes encoding 11 different components of the sarcomere have been identified10–13. Using genetic testing to identify possible mutations may help streamline family evaluation and longitudinal follow up14. After 25 years of genetic testing, however, we are still unable to predict phenotypes and outcomes from a gene-based model. HCM is an extremely heterogeneous disease with regard to clinical onset and presentation, phenotype and clinical course, even within the same pedigree. Both penetrance and expressivity are thought to be influenced by epigenetic and environmental mechanisms, although the quality and extent of these interactions remain elusive.15

In this review we focus on the complex interplay between the genetics and potential modifiers of disease expression including demographic features, physiological challenges such as pregnancy and sports, as well as co-morbid conditions. Some of the potential modifiers (summarized in Table 1) will be used as examples to discuss gene–environment interaction in this particular clinical setting.

**LIFE CYCLE**

**Age**

Although age cannot be considered an environmental factor *sensu stricto*, the effects of aging on the heart are indisputable. In recent years, older patients with HCM have been increasingly recognised due to greater awareness of the disease and advances in cardiac imaging techniques. Young patients appear to have a higher risk of arrhythmic SCD, which is rare in those aged >6016. Such inverse relationship between advanced age and SCD-related risk in HCM inevitably affects management decisions, particularly regarding ICD implantation. Conversely, the burden of disease in terms of atrial fibrillation and heart failure related complications peaks in patients aged 50 to 70 years, due to long-standing microvascular ischemia and progressive myocardial fibrosis leading to remodeling of the LV and LA chambers17. In this regard, while younger patients rarely develop heart failure-related end-points, an early onset of disease is associated with markedly increased risk of HCM complications after mid-life.17

**Pregnancy**

Pregnancy is characterized by significant physiological changes in the cardiovascular system, including increases in cardiac output, extracellular fluid volume and arterial compliance and reduction in blood pressure and total peripheral resistance. Hormonal changes include increased levels of estrogens and progesterone, which result in vasodilatation. A substantial activation of the renin-angiotensin-aldosterone system occurs early in pregnancy and results in increased plasma volume18. These physiological changes also affect the heart, with significant increase in LV wall thickness and mass. Pre-existing cardiovascular disease can therefore be exacerbated by the adaptations that occur during gestation19.

Despite these concerns, pregnancy is well tolerated by asymptomatic or mildly symptomatic women with HCM. The hypertrophied LV can accommodate the rise in cardiac output and blood volume, and the reduction of systemic vascular resistance is generally without consequences on LV filling pressures. Development of heart failure symptoms is uncommon during pregnancy, occurring in <5% of previously asymptomatic HCM patients. The most common issues are related to diastolic dysfunction, LVOT obstruction and arrhythmias. In pregnant HCM patients, pre-existing heart failure symptoms greater than New York Heart Association class II, pulmonary hypertension and severe LVOT obstruction are the main predictors of maternal and neonatal events20. Of note, multiple pregnancies are not likely to affect the natural history of the disease, nor its phenotypic expression3.

**DEMOGRAPHIC FEATURES**

**Ethnicity**

Epidemiological data in different ethnicities show that the prevalence and clinical profile of HCM do not differ among various populations21. Because most of the studies addressing phenotypic expression and natural history of HCM are based on Caucasians, data on individuals of other ethnicities are limited. However, observations in athletes and hypertensive patients reveal that individuals of African/Afro-Caribbean descent show more significant morphological changes, degree of LVH and ECG abnormalities compared with Caucasians22. Awareness of such differences is important in order to avoid over-diagnosis of HCM in healthy individuals exhibiting phenotypes that are within physiological limits for their ethnicity. A recent study by Sheikh et al.23 showed that black patients with HCM almost always exhibit an abnormal ECG, with high prevalence of T wave inversion; moreover, black patients more often had apical or concentric patterns of hypertrophy compared to white patients. Although hypertension is more common in black individuals, the greater burden of LVH does not appear related to hypertension and probably rest on a polygenic basis. Indeed, the morphological differences persisted after excluding hypertensive patients and likely reflect a true impact of ethnicity on the HCM phenotype. In the same study, black patients did not exhibit a higher prevalence of conventional risk markers for SCD and ethnicity was not a determinant of the composite primary outcome of death, cardiac arrest or appropriate ICD therapy.

**Sex**

The Mendelian mode of HCM inheritance is autosomal dominant, which implies that equal numbers of males and females are carriers of the underlying disease-causing mutation. However, males are consistently more prevalent in published cohorts, typically with a 3:2 ratio to females. Although male predominance may reflect a similar lack of awareness that is well recorded in other cardiovascular diseases in women, the difference in disease expression among sexes is likely to be influenced by genetic and endocrine factors. Women with HCM are older at presentation, more symptomatic, and more likely to have resting LV obstruction, compared to men24. While LV mass indexed for body surface area (BSA) is lower in females, suggesting milder phenotypic expression25 (Figure 1), women are more prone to heart-failure related mortality and HCM-related complications26,27. Furthermore, females with HCM have comparable rates of SCD compared to men28,2930, although they may be less exposed to arrhythmic- events triggered by strenuous exercise31,32. As women are less likely to be diagnosed with HCM at routine medical examination, higher index of diagnostic suspicion and lower threshold for referral to a specialist are warranted.

Little is known regarding the impact of sex hormones on the development of myocardial hypertrophy in HCM, although the older, often post-menopausal age at presentation in women with HCM support a protective role of estrogens. Indeed, estrogens are known to have a protective role in secondary hypertrophic response, while exposure of cardiac myocytes to androgens may result in LVH. In healthy individuals, increase in cardiac mass following puberty is greater in men and estrogens have been shown to exert preventive effects on cardiac hypertrophy32. However, the physiological actions of androgens in the heart remained largely unclear compared to those of estrogens. Some studies have shown that androgens are pro-hypertrophic33,35, via a direct androgen-receptors mediated pathway. Furthermore, a study by Lind et al35 showed that variations at the androgen receptor gene was associated with LVH in males with HCM in a cohort of 200 unrelated patients. Furthermore, experiments in mouse models carrying MYBPC3 mutations showed significant sex differences in terms of sarcomeric force generation; these differences were even more evident in mutant mice engaged in an exercise protocol, suggesting that physiological stimuli elicit a sexually dimorphic cardiac response33.

**HABITS AND LIFESTYLE**

**Exercise and Sport**

Regular exercise has a favourable effect on many of the established risk factors for ischemic cardiovascular disease, thereby decreasing morbidity and mortality34–36. However, strenuous exercise is well known to trigger SCD in athletes with an underlying cardiac disease37,38. HCM is one of the most frequent causes of SCD in young athletes39, and the interplay of the pathological substrate characterized by myocardial disarray, fibrosis and microvascular remodelling with physiological mechanical stressors and potentially adverse effects of intense exercise such as dehydration, sympathetic stimulation, electrolyte abnormalities and acid-base disturbances may trigger fatal arrhythmias during exertion40. Therefore, consensus statements recommend that individuals with HCM should refrain from participating in competitive physical activity41,42. These recommendations are based on reasonable pathophysiological assumptions and are ultimately aimed at protecting athletes by preventing SCD.

There are, however, several scientific, epidemiological and ethical matters of debate related to exercise participation in patients with HCM. Firstly, the rate of exercised-induced SCD in HCM is unclear. Recent unpublished data suggest that SCD occurs during sport in less than 20% of SCD victims with a post-mortem diagnosis of HCM, and that young age and male sex are the main independent variables associated with exercise-induced SCD43. Secondly, while HCM has been historically reported as the most common cause of SCD in young athletes in the United States, other conditions as arrhythmogenic right ventricular cardiomyopathy (ARVC) or sudden arrhythmic death syndrome with a normal cardiac autopsy (SADS) may be more frequent 44–46. In recent studies unexplained or “idiopathic” LVH (i.e. LVH without evidence of significant myocardial disarray) has been reported as a relatively common finding in athletes and non-athletes that died suddenly46,47. The significance of “idiopathic” LVH is unclear and postulated theories range from part of the spectrum of HCM, to trigger for fatal arrhythmias in individuals with an underlying arrhythmogenic syndrome, because LVH exacerbates electric instability. These data imply that the epidemiologic burden of HCM as cause of SCD in athletes may be lower than previously reported.

Furthermore, the role of long-term exercise in the natural history of HCM is poorly understood. There are no data to support a detrimental effect of exercise in patients with HCM and no evidence that long-term athletic training may promote an exacerbation of the underlying disease process. In animal models, routine exercise before the development of cardiac phenotype prevented subsequent fibrosis, myocyte disarray, and induction of markers of hypertrophy in mutant myosin heavy chain mice48. Conversely, in rats conditioned to run vigorously for up to 16 weeks, cardiac fibrosis, changes in ventricular function and increased arrhythmic propensity were observed49. To date, none of these effects have been demonstrated in humans, and data on the effects of exercise as a natural history modifier, as seen in arrhythmogenic cardiomyopathy34, are lacking in HCM.

Based on the plethora of benefits of moderate exercise for the cardiovascular system and general well-being, recreational exercise should be encouraged in most individuals with HCM38. At present, most patients are less active than the general population, and report purposefully reducing or even stopping their activity after diagnosis50, an attitude that is likely to adversely affect their long-term outcome. A recent randomized study showed that moderate-intensity exercise, compared with usual activity, resulted in a significant increase in exercise participation and capacity in HCM patients, without a significant increase in the burden of arrhythmias or other adverse events51. This study supports regular adoption of aerobic training in HCM following the Greek philosophical principle of “*Metron ariston (i.e. Moderation is best)”*, based on the tailoring of exercise activity to reasonable thresholds based on age and fitness level.

Another important matter of debate is the management of genotype positive-phenotype negative (G+/P-) individuals, a rapidly increasing population following the widespread adoption of genetic testing. Often, individuals identified by this term have no evidence of LVH, but are not truly “phenotype negative”, due to the presence of ancillary HCM manifestations such as LV crypts, mitral valve abnormalities and mild regional diastolic impairment at the septal level. Although the European Society of Cardiology (ESC) recommendation is restrictive and states that athletes with a G+/P- should have the same limitations as patients with overt HCM, a detrimental role of exercise in these individuals has not been demonstrated52, and their access to competitive sports is not restricted in the US.

**Diet and fluid intake**

The role of dietary habits is crucial to both the development and prevention of cardiovascular disease. Diet and lifestyle have been a main focus of research in coronary artery disease for decades53. Benefits and harms of diet are not limited to the mechanistic interactions underlying the progression of atherosclerosis, but extend to other scenarios, including primary cardiomyopathies. For example, a soy diet was associated with progressive to severe end-stage cardiomyopathy and heart failure in a transgenic mouse model of α-myosin heavy chain HCM, possibly through induction of augmented cell growth and apoptosis. Conversely, such evolution was prevented by a casein diet54. To date, however, the impact of different dietary regimens on patients with HCM has not been investigated.

In clinical practice, apart from the obvious implications related to weight control and cardiovascular prevention, dietary advice to HCM patients should deal with the effects of meals on quality of life and symptomatic status. Following food intake, splanchnic blood flow sequestration results in decreased circulating plasma volume, thereby increasing LV outflow gradients55,56. Thus, post-prandial symptoms of angina, dyspnoea and - occasionally – syncope, are common in obstructive HCM. Patients should be recommended to avoid large meals and reduce levels of post-prandial activity. Dehydration, which results in reduced preload and increased contractility, should also be avoided. Finally, alcohol should be consumed with moderation by HCM patients, as it has been shown to decrease arterial blood pressure and increase systolic anterior motion (SAM) severity and degree of intraventricular obstruction57. (Figure 2)

**ACQUIRED CO-MORBIDITIES**

**Hypertension**

Hypertension is conventionally regarded as a potential exclusion criterion for the diagnosis of HCM3. However, many patients with unequivocal HCM may present with or develop some degree of hypertension, given the high prevalence of hypertension in the adult population58. In most hypertensive patients, LV wall thickness is normal or only mildly increased (≤13 mm). Only a minority of patients, often with secondary forms of hypertension or of Afro-Caribbean or African descent, have more substantial hypertrophy (up to 16 mm) and fall into a “grey zone” of potential overlap with HCM.23 When differentiating hypertensive heart disease from HCM, a number of additional features, including mitral valve abnormalities and lack of extracardiac organ damage may be suggestive of the latter59.

In a recent study, hypertension was an independent predictor of outcome in HCM patients, irrespective of ethnicity, sex or age23. A significant increase in afterload and neuroendocrine activation may further increase LV mass and adversely affect the clinical expression of the disease. Aggressive management of uncontrolled hypertension is therefore mandatory in HCM, but may be challenging, as most vasodilators will exacerbate dynamic left ventricular outflow tract (LVOT) obstruction60,61.

The question of whether a quota of secondary LVH might worsen the phenotypic expression of HCM patients with hypertension remains unresolved. Afterload increase and neuroendocrine activation may plausibly contribute to an augmented LV mass. Likewise, appropriate treatment of hypertension might reduce “non-genetic” LVH. This intuitive concept, although not proven, is supported by studies showing regression of LVH following septal reduction therapies. Of note, reduction of LV mass following resolution of afterload mismatch occurred in regions of HCM hearts remote from the septum, suggesting that reverse remodelling may occur in this disease upon removal of pathologic environmental stimuli62,63. This general concept of partial reversibility of “secondary” LVH in HCM patients requires further investigation and is of relevance to other potential determinants such as sport, obesity and renal failure.

Another interesting concept is that polymorphisms in the renin–angiotensin– aldosterone system (RAAS), which have been associated with LVH in untreated hypertension, may be potential disease modifiers in HCM64. While the role of RAAS polymorphisms in HCM has not been clearly established, it is possible that selected genotypes may specifically impact the clinical phenotype of HCM65.

**Obesity**

Obesity is a rising public health problem, and a known risk factor for cardiovascular diseases. Because of its maladaptive effects on various cardiovascular risk factors and its adverse effects on cardiac structure and function, obesity has a major impact on morbidity and mortality. As recently demonstrated, its prevalence in HCM is remarkably high, reaching almost 40%, likely due to excessive exercise restriction following the diagnosis. Obesity is independently associated with increased LV mass, (Figure 3) an adverse prognostic factor in HCM, contributing to more rapid clinical progression and worsening of heart failure symptoms66. Interestingly however, LV mass increase in obese HCM patients seems to merely reflect LV cavity enlargement, physiologically aimed at increasing cardiac output67 to meet the increased requirements of excessive body weight. Conversely, maximal LV thickness is similar in normal weight vs obese HCM patients, suggesting that the genetic design of asymmetric septal LVH is independent of body mass index (BMI)50. Of note, LV obstruction is more common in obese patients and observed in more than 50% with BMI >30, because of distinctively higher predisposition to provocable (as opposed to resting) gradients. A beneficial impact of weight reduction on the severity of LVOT obstruction is plausible but remains unproven68. Finally, although the role of obesity as an independent risk factors for SCD in HCM has not been established, the susceptibility of obese patients with HCM to fatal arrhythmias is a potential area of research69.

**Obstructive Sleep Apnoea**

Obstructive sleep apnoea (OSA) is a common condition in Western countries, characterized by repetitive interruption of ventilation and hypoxia during sleep, which affects a large proportion of patients with hypertension, obesity, CAD, atrial fibrillation and stroke. In *peripheral* OSA this is caused by collapse of the pharyngeal airway, while *central* OSA is related to malfunction of the respiratory control centers in the brainstem.

In recent years there have been rapid advances in the understanding of the relation between OSA and cardiovascular disease, including HCM70. OSA has been reported in up to 70% of patients with HCM71. LVOT obstruction is generally exacerbated by sympathetic stimulation and the nocturnal hypoxia-induced hyperadrenergic state characteristic of OSA would be expected to worsen the haemodynamics of HCM. This vicious pathophysiological cycle translates in increased symptom burden during the day. Furthermore, peripheral vasoconstriction, apnoea-induced hypoxemia, carbon dioxide retention, renal retention of salt and water, and increased renin-angiotensin-aldosterone activity may contribute to arrhythmogenesis in an already vulnerable pathological substrate72. Whether OSA is associated with higher rate of ventricular arrhythmias or SCD and in general with adverse prognosis in HCM remains unclear. Nevertheless, treatment of sleep apnoea, whether by weight loss, continuous positive airway pressure (CPAP) or postural therapy provides important benefit in the general population, and should be sought in patients with HCM.

**Coronary artery disease**

Myocardial ischemia is often observed in patients with HCM, occurring at the microvascular level as a result of structural abnormalities of the intramural coronary arterioles, characterized by thickening of the intima and medial layers of the vessel wall associated with decreased luminal cross-sectional area73,74. Adult patients with HCM are not immune from epicardial CAD, which may be difficult to diagnose, given the high frequency of microvascular angina and the striking ECG repolarization abnormalities present at rest, which hinder the interpretation of exercise ECG testing. Concomitant atherosclerotic disease has an important impact on the natural course of HCM. Given the increased myocardial mass and high myocardial oxygen demand, HCM patients are particularly susceptible to the additional ischemic burden of one or multiple epicardial coronary artery stenosis75. Not unexpectedly, CAD is a major prognostic indicator in HCM and it is associated with an increase in overall mortality, SCD and cardiac events, with a synergistic, rather than additive, effect58. Preventive strategies for atherosclerotic disease should always be considered in HCM patients and the standards for control of modifiable CV risk factors should arguably reflect those used for secondary, rather than primary prevention of CAD, due to the intrinsic frailty of the HCM myocardium to ischemic insults.

Myocardial bridging is a rare but modifiable mechanism of ischemia, acute myocardial infarction, and even SCD, in young HCM patients76. Myocardial bridging occurs when the epicardial coronary arteries, usually the proximal LAD, are intra-myocardial, resulting in systolic compression of a coronary artery on coronary angiography. While bridging occurs also in normal healthy controls, it is much more common in HCM, reaching a prevalence of 30-40%. Because only a fraction of these lesions have been associated with SCD, generally in children, the role of bridging as a risk predictor in adult patients is debated but probably limited. Only when associated with clear hemodynamic abnormalities and symptoms, myocardial bridging should be treated with a surgical deroofing procedure77.

**SARCOMERE PROTEIN GENE PROFILE AND PREDISPOSITION TO CARDIAC DISEASE**

Sarcomere gene mutations have been identified in the general population by large scale screening studies. Most carriers do not have a cardiomyopathy and may express no or only mild and non-specific phenotypic stigmata. However, these variants seem to retain a generic capacity to trigger cardiac disease in the presence of environmental stimuli, creating a sort of non-specific frailty of the myocardium. In a landmark study, a common 25 mb MYBPC3 deletion was associated with increased risk of heart failure in South Asians exposed to secondary risk factors, such hypertension and hypercholesterolemia, posing a lifelong threat to carriers78. Furthermore, a role for truncating titin mutations has been recently proposed in the development of peri-partum cardiomyopathy79, suggesting the possible interaction between a genetic predisposition and additional environmental (pregnancy) or genetic stimuli. These observations add a broader dimension to the interactions between cardiomyopathies and the environment: from relatively uncommon, genetically-driven diseases that are only modestly influenced by external stimuli, to a common genetic trait that is not pathogenic *per se*, but may provide predisposition to cardiac disease in the presence of risk factors and high-risk lifestyles (Figure 4). Understanding these complex interactions may prove critical to the identification of novel therapeutic targets for CV disease in the next future.

**CONCLUSIONS AND FUTURE PROSPECTIVES**

Our [genetic](https://www.boundless.com/psychology/definition/genetics/) destiny is hardly written in stone. Virtually all human diseases result from the interaction of genetic susceptibility factors with modifiable environmental influences. When we observe that even “classic” inherited diseases can be modified by environmental conditions, it becomes clear that the relationship between the two is much more complex than a simple one-gene – one disease model linear relationship. HCM is not an exception to this general rule. Overall, however, physiological stimuli and co-morbidities seem to exert a modest impact on the phenotypes of HCM, its natural history and outcome. Therefore, future research targeting HCM variability should rather focus on molecular aspects including modifier genes, epigenetic factors and role of regulatory systems such as MiRNAs, the ubiquitine-proteasome complex or nonsense-mediated RNA decay80,81.

Nevertheless, identifying modifiable risk factors which may aggravate HCM phenotype and clinical course remains important in clinical practice, even in absence of specific studies, along the general principles of contemporary CV medicine. Because of the intrinsic fragility of HCM hearts, it may be reasonable to manage patients according to the standards of established atherosclerotic disease, i.e. of secondary rather than primary cardiovascular prevention, including strict targets for lipid profile, blood pressure and weight control, and lifestyle advice including appropriate exercise and diet (Table 2).

In the era of evidence-based medicine, the conundrum behind gene-environment interactions in genetic inherited cardiac diseases should be unravelled through improved access to empiric knowledge from randomized control trials, as well as, increasingly, from Big Data82; extensive research is warranted to identify environmental factors that may effectively act as natural history modifiers. Only through a deepened understanding of this interplay we will be able to address the many questions related to the extreme heterogeneity of clinical expression and natural history of HCM.

**Conflict of Interest Disclosures**: None

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**Figure legends:**

**Figure 1.** Sex differences in LV mass in patients with HCM. Male patients exhibit significant higher values of indexed LV mass. Adapted from Olivotto et al. [Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy.](https://www.ncbi.nlm.nih.gov/pubmed/18687251) J Am Coll Cardiol. 2008; 52(7):559-66. Abbreviations: LV: left ventricular.

**Figure 2.** Alcohol and LV obstruction in HCM. After ethanol ingestion the average LV gradients increase from an average of 38.1 to 62.2 mmHg. Adapted from Paz et al. [The effect of the ingestion of ethanol on obstruction of the left ventricular outflow tract in hypertrophic cardiomyopathy.](https://www.ncbi.nlm.nih.gov/pubmed/8782501) N Engl J Med. 1996 ;335(13):938-41.

**Figure 3.** Relationship between LV mass and body mass index (BMI) (A) and LV mass indexed for body surface area (BSA) and BMI (B) in patients with HCM. Obese individuals (BMI >30) exhibit higher values of LV mass and indexed LV mass. Adapted from Olivotto et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013; 62(5):449-57. Abbreviations: BMI: body mass index; LV: left ventricular.

**Figure 4.** Continuum betweengenetic predisposition and environmental influences in HCM. Multiple variants have usually a very severe phenotypic expression that is less likely to be dependent from environment, while in individuals harbouring a single mutation the effect of other acquired conditions may be more relevant. Multiple variants, each with small effect size, may interact with non-genetic factors to produce an HCM phenotype. Genetic variants recognized as pathogenic may be present in healthy individuals where the phenotypic expression emerge only after the interaction with a specific environmental factor.

**Table 1.** Potential environmental modifiers of phenotypic expression in HCM.

|  |  |  |
| --- | --- | --- |
| **Phenotypic expression** | **Modifiers** | **Effects** |
| **LV HYPERTROPHY** | Sex | ↑LVH in males |
| Ethnicity | ↑LVH in Afro-Caribbean  athletes |
| Obesity | ↑LV mass in obese individuals |
| Hypertension | ↑LVH in hypertensive pts |
| Renal disease | ↑LVH in CKD |
| Sport | No clear effects |
| Diet | No clear effects |
| **MICROVASCULAR DYSFUNCTION** | Hypertension | ↑ microvascular ischemia |
| Auto-immune disease | ↑ microvascular ischemia |
| CAD | ↑ micro and macrovascular ischemia |
| Cocaine abuse | ↑ micro and macrovascular ischemia |
| Thrombophilic status | ↑ micro and macrovascular ischemia |
| **HEMODYNAMIC STATUS / OBSTRUCTION** | Dehydration | ↓ venous return,↑ LV gradients |
| Anaemia | ↑ LV gradients |
| Thyroid disease | ↑ LV gradients |
| Pregnancy | ↓ LV gradients |
| Pharmacological treatment (inotropes, vasodilators, diuretics) | ↑ LV gradients |
| Acquired valvular heart disease | ↑↓ LV gradients |

**Abbreviations:** CAD: coronary artery disease; CKD: chronic kidney disease; LAD: left anterior descending artery; LV: left ventricular; LVH: left ventricular hypertrophy.

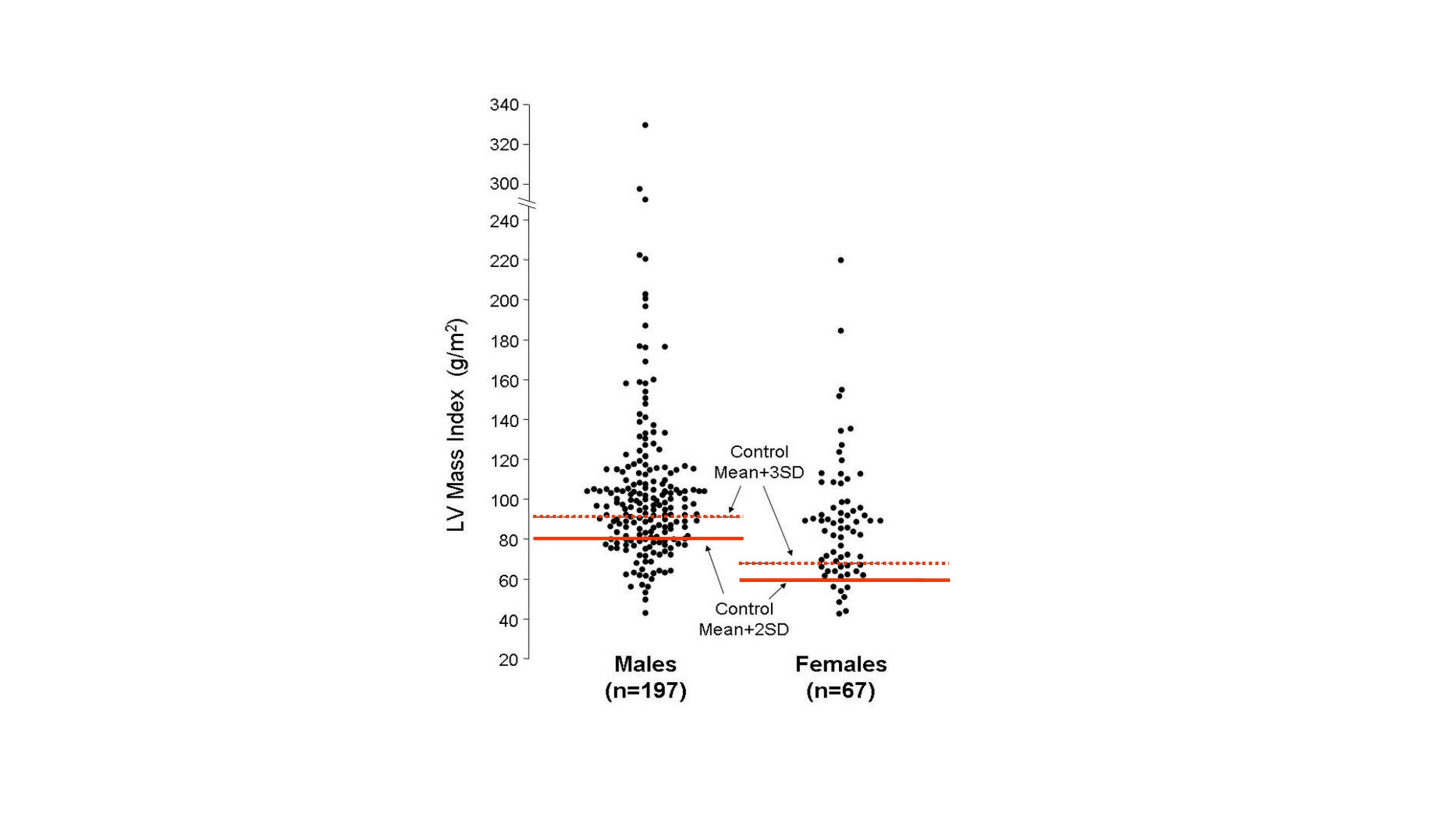
**Table 2.** Proposed management of modifiable risk factors in patients with HCM

|  |  |
| --- | --- |
| **Lifestyle/clinical variables** | **Possible Effects** |
| LDL < 100 mg/dl\* | ↓ risk of CAD and myocardial ischemia |
| BP < 130/80 mmHg\* | ↓ risk of secondary LVH due to increased afterload |
| Moderate exercise | Improvement in diastolic function and exercise capacity  ↓ risk of obesity |
| Weight management | ↓ risk of obesity  ↓ risk of development of a more marked LVH due to increased afterload |

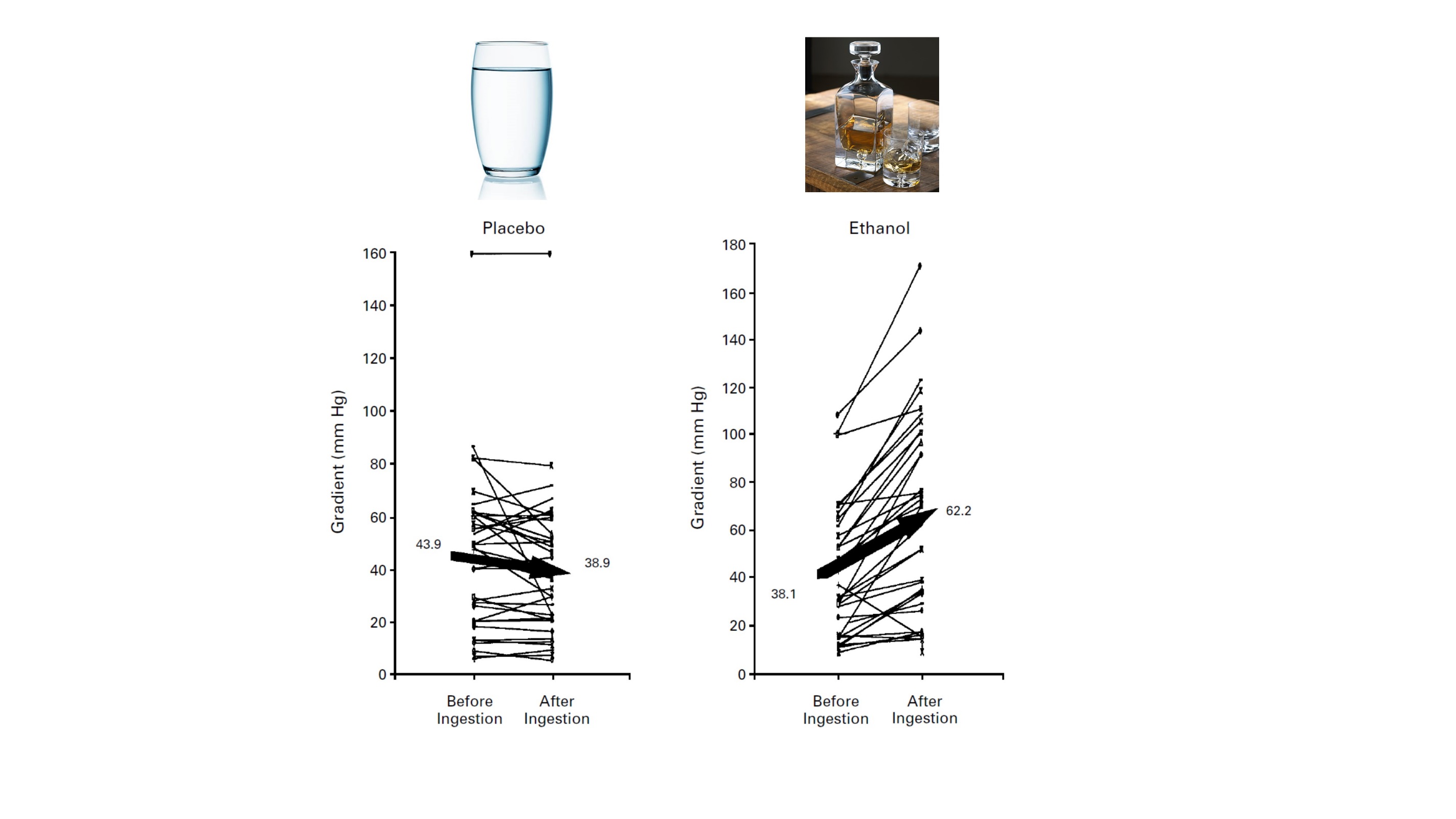
**Symbols**: \*=The standards for control of modifiable CV risk factors should arguably recapitulate those used for secondary prevention in CAD patients, in all genetic cardiomyopathies, based on the principle that superimposed atherosclerotic disease seems to have synergistic, rather than additive, effects.

**Abbreviations:** BP: blood pressure; LDL: low-density lipoprotein.

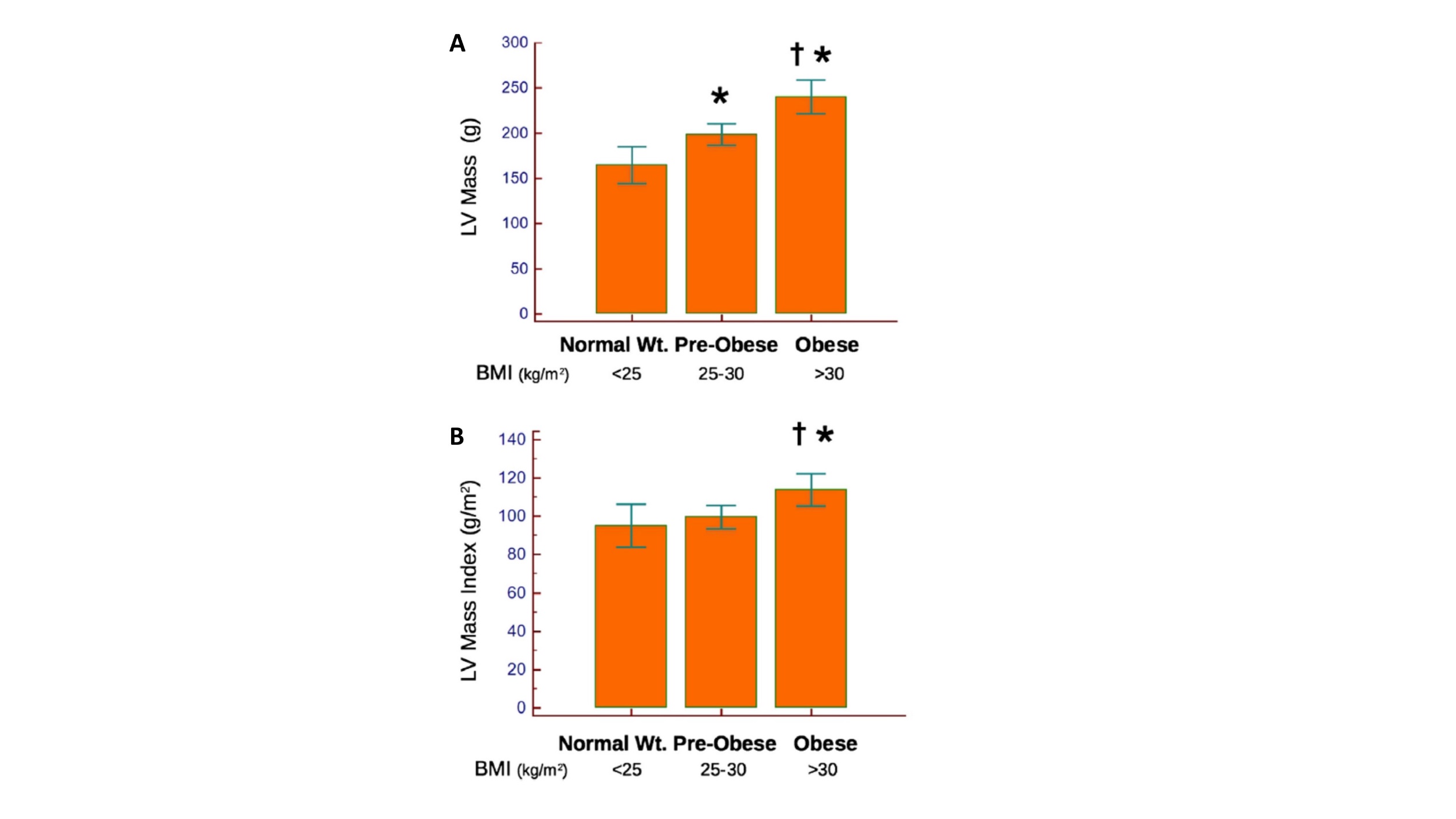
**Figure 1.**



**Figure 2.**

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**Figure 3.**



**Figure 4.**

