

# Titel: Reported physical symptoms during screening echocardiography is not associated with the presence of suspected hypertrophic cardiomyopathy.

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## Abstract

**Background:** The prevalence of hypertrophic cardiomyopathy (HCM) can be silent and can present with sudden death as the first manifestation of this disease. The goal of this study was to evaluate any association between reported physical symptoms with the presence of suspected HCM. **Method:** The Anthony Bates Foundation has been performing screening echocardiography across the United States for the prevention of sudden death since 2001. A total of 4,120 subjects between the ages of 6 and 79 underwent echocardiographic screening. We evaluated any association between any symptoms and suspected HCM defined as any left ventricular wall thickness [?] 15 mm. **Results:** The total prevalence of suspected HCM in the entire study population was 1.1%. The presence of physical symptoms were not associated with HCM (chest pain in 4.3% of participant with HCM vs. 9.9% of the control,  $p=0.19$ , palpitation in 4.3% of participant with HCM vs. 7.3% of the control.,  $p=0.41$ , shortness of breath in 6.4% of participant with HCM vs. 11.7% of the control.,  $p=0.26$ , lightheadedness in 4.3% of participant with HCM vs. 13.1% of the control.,  $p=0.07$ , ankle swelling in 2.1% of participant with HCM vs. 4.0% of the control.,  $p=0.52$ , dizziness in 8.5% of participant with HCM vs. 12.2% of the control.,  $p=0.44$ ). **Conclusion:** Echocardiographic presence of suspected HCM is not associated with a higher prevalence of physical symptoms in the participants undergoing screening echocardiography. This finding confirmed that HCM can be asymptomatic in many patients and a questionnaire cannot distinguish the HCM population from a control group.

**Titel: Reported physician symptoms during screening echocardiography is not associated with the presence of suspected hypertrophic cardiomyopathy.**

**Short title: Symptoms in suspected HCM**

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**Results:** The total prevalence of suspected HCM in the entire study population was 1.1%. The presence of physical symptoms were not associated with HCM (chest pain in 4.3% of participant with HCM vs. 9.9% of the control,  $p=0.19$ , palpitation in 4.3% of participant with HCM vs. 7.3% of the control,  $p=0.41$ , shortness of breath in 6.4% of participant with HCM vs. 11.7% of the control,  $p=0.26$ , lightheadedness in 4.3% of participant with HCM vs. 13.1% of the control,  $p=0.07$ , ankle swelling in 2.1% of participant with HCM vs. 4.0% of the control,  $p=0.52$ , dizziness in 8.5% of participant with HCM vs. 12.2% of the control,  $p=0.44$ ).

**Conclusion:** Echocardiographic presence of suspected HCM is not associated with a higher prevalence of physical symptoms in the participants undergoing screening echocardiography. This finding confirmed that HCM can be asymptomatic in many patients and a questionnaire cannot distinguish the HCM population from a control group.

## Introduction:

Hypertrophic cardiomyopathy (HCM) is a cardiac condition that is defined by hypertrophy of the left ventricle, hypercontractility, decreased compliance, and poor relaxation (1-3). HCM presents as a progressive and chronic condition that may become devastating and life-changing, affecting the quality of life dramatically. Chest pain, palpitations, exertional dyspnea, shortness of breath, ankle swelling, fatigue, dizziness, lightheadedness, and syncope are the most common symptoms identified (2-5). Sudden cardiac death (SCD), Heart failure (HF), atrial fibrillation (AF), and stroke are all related to HCM (6-8). Symptoms might be mistaken with those of other diseases, and an accurate diagnosis may take years. The assumed prevalence is approximately 1:500 adults (9), however only around 100,000 among the estimated 700,000 HCM patients in the United States have been diagnosed (10). Many asymptomatic HCM patients are diagnosed accidentally or through screening (3). Clinical history comprises a complete cardiac history and a 3-generation family history for determining HCM or sudden death relatives (3, 11, 12). Functional and fitness capacity assessment, focusing on training regimen and exertion symptoms—chest pain, palpitations, dyspnea, and syncope (3, 13).

Significant advancement seems to have been achieved in comprehending the disease from both genetic and clinical perspectives (14), although methods of diagnosis have improved (15). Despite genotype positive-phenotype negative people have not been included into HCM prevalence estimations, these individuals are at an elevated risk of acquiring the disease, however, the progression to clinically severe disease remains unpredictable [8,9,10].

By improving timely treatment, proper prognostic classification, and earlier diagnosis can allow for an overall decrease in disease-related mortality/morbidity (16). When it was originally discovered, HCM was considered

to be an uncommon disease that largely affected young people and had a poor prognosis due to the potential risk for SCD (17, 18). Currently, it is understood that HCM may impact patients of any age whereas the overall prognosis of a diagnosed HCM patient is usually favorable, with about two-thirds enjoying an ordinary lifespan with almost no morbidity and an average HCM-related mortality that is approximately 0.7%/year (19-21). Some patients, however, are at an elevated risk of SCD or developing atrial fibrillation (AF)/heart failure (HF). As a result, identifying these individuals is a critical priority (2, 22).

Echocardiography is the gold standard for HCM screening, diagnosis, follow-up, and prognostic classification (2, 22, 23). Recent SCD risk calculators authorized by the AHA and the ESC (2, 22), include echocardiographic measures. Advanced echocardiographic techniques (two-dimensional speckle tracking, tissue Doppler) are able to distinguish HCM from different causes of hypertrophy and recognize people who are susceptible to developing HF or SCD. 3D echocardiography provides greater information about hypertrophic distribution, the mechanism of dynamic LV obstruction, and LV mass (23).

Our study aims to explore the connection, between reported symptoms and suspected HCM (Hypertrophic Cardiomyopathy) during echocardiographic screening. While echocardiography is a tool we believe it could be more useful if we can determine whether specific symptoms are linked to a higher likelihood of detecting HCM. By understanding the relationship between symptoms and suspected HCM we can improve risk assessment. Our main objective is to contribute to the growing body of knowledge about HCM, which will lead to more effective practices and earlier detection of this life-threatening condition.

## **Materials and Methods:**

### **The study population:**

Since its establishment, in 2001 the Anthony Bates Foundation has played a leading role in efforts to prevent cardiac death through echocardiographic screening. For this cohort study, we examined data collected as part of this initiative. A total of 4,120 individuals ranging in age from 6 to 79 years participated in screening across regions of the United States. The study was a retrospective study of that was approved by the institutional review board with exempt status.

### **Data collection:**

Prior to receiving an echocardiogram, everyone was required to complete a questionnaire about their health symptoms. The questionnaire included the symptoms of shortness of breath, chest pain, dizziness, fatigue, and palpitations. Participants had to answer questions about all symptoms, whether mild or common. Informed consent was obtained to participate in the screening. Individuals less than 18 years of age needed parental informed consent. Echocardiography was performed by many donated handheld echocardiography devices and the final diagnosis was confirmed by volunteer cardiologists.

### **Echocardiographic assessment:**

Our main objective was to investigate the link between self-reported symptoms and the presence of suspected Hypertrophic Cardiomyopathy (HCM). To identify cases with suspected HCM we employed the accepted criterion of a ventricular wall thickness [?] 15 mm, which is an important diagnostic indicator for this heart condition.

### **Statistical analysis:**

We conducted an analysis to examine the correlation, between self-reported symptoms and the presence of suspected HCM. We evaluated the strength and significance of this relationship using techniques such as regression and chi-square tests. Age, gender, and other related demographic factors were also considered as variables that could impact the outcomes of our analysis.. We used SPSS version 17 for our data. A p-value of < 0.05 is deemed significant.

### **Result :**

The demographic data of patients including age, sex, and race have been evaluated. The age range of the participants was between 4 and 74 years, and most of the individuals were 18, 16, and 17 years old, respectively (Figure .1). Male gender were the majority of the participant. (Figure .2).

The overall prevalence of possible HCM was found to be 1.1% throughout the entire population. There was no correlation between HCM and the occurrence of any physical symptoms. Chest pain in 4.3% of participants with HCM vs. 9.9% of the control,  $p=0.19$ , palpitation in 4.3% of participants with HCM vs. 7.3% of the control.,  $p=0.41$ , shortness of breath in 6.4% of participant with HCM vs. 11.7% of the control.,  $p=0.26$ , lightheadedness in 4.3% of participant with HCM vs. 13.1% of the control.,  $p=0.07$ , ankle swelling in 2.1% of participant with HCM vs. 4.0% of the control.,  $p=0.52$ , dizziness in 8.5% of participant with HCM vs. 12.2% of the control,  $p=0.44$  (Figure .3). Our findings suggest that based on this study's population symptoms reported during echocardiography screening may not serve as indicators, for detecting the presence of HCM.

## Discussion:

We investigated the link between reported symptoms and suspected HCM in our study. The findings are remarkable because they call into question what we thought we knew and provide light on how difficult it can be to diagnose this disorder. In summary, 1.1% of the population had suspected HCM. Physical symptoms were not associated with HCM (chest pain in 4.3% of participants vs. 9.9% of the control,  $p=0.19$ , palpitation in 4.3% vs. 7.3%,  $p=0.41$ , shortness of breath in 6.4% vs. 11.7%,  $p=0.26$ , lightheadedness in 4.3% vs. 13.1%,  $p=0.07$ , ankle swelling in 2.1% vs. 4.0%,  $p=0.52$ , dizziness According to our findings, several physical symptoms such as chest pain, palpitations, shortness of breath, lightheadedness, ankle edema, and dizziness do not correlate with the existence of HCM, as validated by echocardiography. This discovery has far-reaching implications for HCM diagnosis and management.

The primary takeaway from our research is that symptoms linked with HCM should not be used to as the main, primary, and only way of diagnosing the disease. Rather, our data indicate that a comprehensive screening and diagnostic approach is required, and also it was presented that cardiac imaging is used to make diagnoses and clinical recommendations for HCM patients (3), while echocardiography is the primary imaging modality for the majority of patients (3), Cardiac Magnetic Resonance (CMR) imaging can enhance or replace it in unclear cases, additionally imaging can confirm (or rule out) alternative diagnoses, assess phenotypic severity, and identify structural cardiac abnormalities (e.g., valvular, systolic, and diastolic function) through the American College of Cardiology/American Heart Association recommendation in 2020 by Ommen et al.(3). This conclusion is significant given the prevalence of HCM in the population and the possible hazards of sudden cardiac death, furthermore, HCM contributed to one in every thirty SCAs among the young and middle-aged overall population, resulting in a yearly SCA prevalence ranging from 0.2% to 0.3% in unselected HCM patients in the community through study by Aro et al.(25) in 2017. The preliminary diagnosis of HCM had been missed in the great majority of SCA cases prior to cardiac arrest (25). The low predicted risk of SCA among young together with middle-aged HCM patients, on the other hand, demonstrates the disease's generally benign course in the great majority of people who are affected (25), and also it was claimed in large clinic population studies performed by Cannan et al. (26) and Kofflard et al. (27), Unfortunately, SCD continues to be of considerable concern. It could be the disease's earliest symptom, especially in competitive and young athletes which were declared in a large registry study over US conducted by B. J. Maron et al. (28), and accompanying consequences even in individuals with no obvious symptoms, in the context of the situation that a substantial portion of HCM patients have been discovered to have asymptomatic or the least potential symptoms if their echocardiogram confirmed HCM disease which was conducted by Udelson et al(29). and O'Gara et al. (30), although through retrospective cohort in 2017 by Rowin et al.(31) this point declared that the majority of patients (70%) seemed asymptomatic or slightly symptomatic according to New York Heart Association (NYHA) classifications one and two (31), also in a large community-based study have done by Kofflard et al.(32) in 2003 (44%) of patients were asymptomatic (32).

Because this disorder can run in families, screening those with a family history of HCM or those who have SCD is critical. While family history is still used in screening, our research demonstrates that focusing solely

on symptoms is not a reliable method of identifying persons with HCM. In studies conducted by Miller et al. (33) in 2013 and Tomašov et al. (34) in 2014, It was demonstrated that HCM patients and relatives verified the value of genetic testing according to the management of close relatives and discovered that the suggested echocardiographic parameters had only a limited advantage for recognizing causes of disease mutation carriers (33, 34). In terms of detection and screening, echocardiography is the gold standard (2, 22, 23). Our findings highlight the need to use echocardiography to confirm HCM in people who have symptoms of the illness. Echocardiography is a reliable approach for detecting HCM (3). It is critical in avoiding delayed or inaccurate diagnoses (3, 25).

In the screening, diagnosis, follow-up, and prognostic categorization of HCM, echocardiography is considered to be the gold standard (2, 22, 23). Recent risk calculators for SCD that have been approved by the AHA and the ESC (2, 22) contain echocardiographic measures. Innovative echocardiographic techniques, such as two-dimensional speckle tracking and tissue Doppler, are able to differentiate hypertrophy caused by HCM from that caused by other conditions and identify individuals at risk of developing HF or SCD. A greater amount of information can be obtained using 3D echocardiography about hypertrophic distribution, the cause of dynamic LV obstruction, and LV mass (23).

When identifying HCM with echocardiography, we focus on a set of symptoms rather than just looking at symptoms, which is an important part of our study. This method allows us to assess how symptoms and disease are related, which increases the importance of our research. It provides insight into whether or not various symptoms are associated with HCM.

In contrast to previous studies, our study takes into account a wide variety of ages has a big sample size, and represents that the participants ranged in age from 4 to 74 years old, with the majority of them being 18, 16, and 17 years old. There were fewer African-Americans than other races, and there were more men than women, although HCM is age dependant and might include racial/ethnic disparities depending on whether clinically or subclinical evident instances are evaluated (35). However, in a study done by Maron et al.(10) in 20 the mean age of HC diagnosis was about the fifth decade of life, with women constituting 43% of the overall HC cohort(10), This increases the applicability and relevance of our findings to patient populations. Taking this approach allows us to acquire a better understanding of the relationship between symptoms and HCM, providing useful insights for distinct patient groups.

Because of the overlap of symptoms with systemic diseases, diagnosing HCM can be difficult. Symptoms such as chest pain, palpitations, shortness of breath, lightheadedness, ankle swelling, and dizziness can be caused by a variety of illnesses, some of which are benign. This overlapping symptomatology can make it difficult to diagnose HCM quickly. The highlighted importance of metabolic storage disorders or inborn errors of metabolism (IEM) such as Glycogen storage disorders including Danon disease, PRKAG2 cardiomyopathy, Pompe disease (glycogen storage disease type 2), and Forbes disease (glycogen storage disease type 3), also lysosomal storage disorders like Anderson-Fabry disease, furthermore mitochondrial cytopathies, cardiac amyloidosis that could mimic HCM ('HCM phenocopies') (36, 37).

The most prevalent symptoms are chest pain and dyspnea (38). Due to diastolic dysfunction, elevated LV end-diastolic pressure can produce dyspnea, especially during exercise (38). Myocardial hypoperfusion and oxygen demand can induce chest pain. Palpitations are prevalent and can cause syncope and dizziness (38). Syncope is rare but serious because it commonly precedes SCD. (32, 39). However, through a case report by Elsouri et al. (40) in 2023, the two-dimensional technique failed to capture septal hypertrophy many times (40). In this scenario, three-dimensional methods like cardiac MRI showed enhanced sensitivity and specificity. In patients between 40 and 70 with, dizziness, dyspnea on exertion (DOE), and chest pain, the HCM should be considered, and cardiac MRI should be performed if symptoms recur after TTE imaging shows no abnormalities (40), according to the only study conducted on a case report in 2023 (40), our study, due to the large sample size examined, its results are very important for clinical experts in diagnosis and treatment and potentially a great help to the health-policy makers to formulate Early detection and screening programs will prevent mortality and complications of HCM.

Our discoveries have consequences. The fact that these common symptoms do not always signal the presence of HCM highlights the importance of a screening approach. Symptoms alone may not be sufficient, and further measures such as screening or regular echocardiograms for at-risk patients may be required. Individuals may remain asymptomatic until they are discovered through screening or when consequences occur in some cases. This emphasizes the significance of complete screening for those who are at risk even in the absence of symptoms.

### Limitations:

Despite the significance of our findings, it is critical to acknowledge our study's limitations. Retrospective cohort studies, by definition, include data collection limits and potential biases. Furthermore, our study focused on symptoms and their relationship to HCM without taking clinical or genetic factors into account. In the future, research must address these limitations and go deeper into the complexities of HCM diagnosis and management.

### Conclusion:

To summarize, our study challenges the approach to diagnosing HCM by demonstrating that certain symptoms do not always suggest a diagnosis of HCM via echocardiography. This discovery has far-reaching consequences, underscoring the importance of a multimodal strategy to screening for HCM in high-risk people. This strategy should include genetic screening and routine echocardiography. Early detection and treatments continue to be critical in reducing disease progression, sudden cardiac death, and related consequences. While our work provides some insight into this issue, more research is needed to improve our understanding of HCM and its diagnosis and to have ideal and more practical screening.

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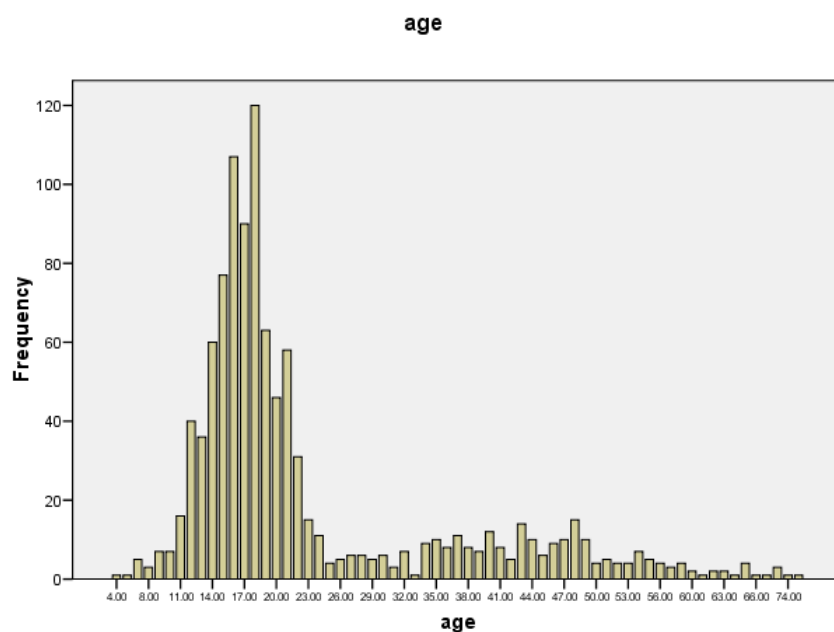


Figure . Age of the study population

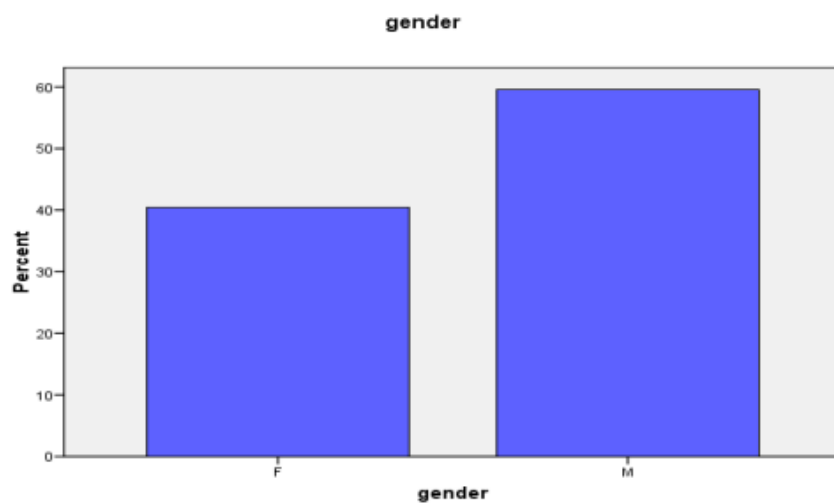


Figure 2. Demographics of the screened population: Gender

