

# Mortality Risk of Untreated Myosin-Binding Protein C–Related Hypertrophic Cardiomyopathy

## Insight Into the Natural History

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- Objectives** The goal of this study was to assess the mortality of hypertrophic cardiomyopathy (HCM), partly in times when the disease was not elucidated and patients were untreated.
- Background** HCM is feared for the risk of sudden cardiac death (SCD). Insight in the natural history of the disorder is needed to design proper screening strategies for families with HCM.
- Methods** In 6 large, 200-year multigenerational pedigrees (identified by using genealogical searches) and in 140 small (contemporary) pedigrees (first-degree relatives of the proband) with HCM caused by a truncating mutation in the myosin-binding protein C gene ( $n = 1,118$ ), we determined all-cause mortality using the family tree mortality ratio method. The study's main outcome measure was the standardized mortality ratio (SMR).
- Results** In the large pedigrees, overall mortality was not increased (SMR 0.86 [95% confidence interval (CI): 0.72 to 1.03]), but significant excess mortality occurred between 10 and 19 years (SMR 2.7 [95% CI: 1.2 to 5.2]). In the small families, the SMR was increased (SMR 3.2 [95% CI: 2.3 to 4.3]) and excess mortality was observed between 10 and 39 years (SMR 3.2 [95% CI: 2.3 to 4.3]) and 50 and 59 years (SMR 1.9 [95% CI: 1.4 to 2.5]).
- Conclusions** We identified specific age categories with increased mortality risks in HCM families. The small, referred pedigrees had higher mortality risks than the large 200-year multigenerational pedigrees. Our findings support the strategy of starting cardiological and genetic screening in the first-degree relatives of a proband from 10 years onward and including persons in the screening at least until the age of 60 years. Screening of more distant relatives is probably most efficient between 10 and 19 years. (J Am Coll Cardiol 2011;58:2406–14) © 2011 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disorder. The prevalence (1:500) is relatively high, and HCM is the most common cause of sudden cardiac death (SCD) in those age younger than 35 years and in young athletes (1,2). The overall annual mortality rate of the disease is approximately 1% (3–6).

In patients with HCM, up to 30% of the mutations are detected in the myosin-binding protein C (*MYBPC3*) gene (7–11). Most of these mutations are nonsense or frameshift mutations that are supposed to result in truncated proteins, suggesting haploinsufficiency (9,12,13). Almost 25% of the Dutch patients with HCM carry the c.2373dup (originally

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described as c.2373\_2374insG, p.Trp792ValfsX41) founder mutation in *MYBPC3* (14). Initially, the phenotype of *MYBPC3* mutation carriers was considered to be mild (15–18); however, there is increasing evidence that definite genotype–phenotype correlations cannot be made. Hypertrophy and symptoms can develop at any age, and the clinical course of the disease shows large variation: having a lifelong asymptomatic course is not an exception, but SCD at a young age, heart failure, and embolic stroke have also been observed among carriers of *MYBPC3* mutations (8,19–21).

The identification of HCM-causing mutations has promoted DNA-testing of probands and, subsequently, of relatives. Family screening increasingly identifies asymptomatic carriers, who have an ill-defined mortality risk. According to worldwide consensus, the risk of SCD in HCM patients and of asymptomatic mutation carriers should be assessed frequently on the basis of a small number of readily determined clinical parameters (3). However, traditional risk factor studies were mainly based on patients, not on individuals detected by family screening (22,23). Therefore, essential information is lacking to establish reliable recommendations for follow-up, prophylactic interventions in asymptomatic carriers, and to perform optimal family screening. Insight into the natural history of the disorder is therefore needed to design proper cardiological and genetic screening strategies for families with HCM (24–28).

In the present study, we assessed the natural history with the family tree mortality ratio (FTMR) method in large multigenerational pedigrees with untreated HCM patients and in a large number of small (contemporary) pedigrees (all first-degree family members of a proband) who visited 2 tertiary cardiogenetic clinics in the Netherlands (29,30).

## Methods

**Subjects and genealogical searches.** We recruited a total of 148 apparently unrelated consecutive HCM patients (probands) with a truncating *MYBPC3* mutation who were evaluated in the cardiogenetics/cardiovascular outpatient clinics in the University Hospitals in Amsterdam and Rotterdam between 1996 and 2009. A complete family history was ascertained in 140 probands; for 8 probands, we were unable to collect the date of birth and death of all first-degree relatives. The identified mutations are described in Table 1. Of these 140 patients, 94 (67%) were carriers of the c.2373dup (p.Trp792ValfsX41) mutation. They all shared an identical haplotype of the *MYBPC3* gene, suggesting a common founder approximately 25 generations ago (14). We performed genealogical searches with the official records of births, marriages, and deaths. These data are very well preserved in the Netherlands and have been collected irrespective of socioeconomic status starting 200 years ago. We traced maternal and paternal ancestors of the probands throughout as many generations as possible, and we were able to link 12 probands (with the c.2373dup

mutation) to 6 pairs of common ancestors. Subsequently, we traced all first-degree relatives (50% carriers) of the persons on the transmission line (obligate carriers) and collected data on births and deaths of these persons. We thus collected 6 large, 200-year multigenerational pedigrees.

In addition, we collected data on births and deaths of all first-degree relatives of 140 probands referred to our University Hospitals. These small (contemporary) pedigrees consisted of all first-degree relatives of 94 probands with the c.2373dup mutation, 24 small families with the c.2827C>T (p.Arg943X) mutation, 11 with the c.2864–2865delCT (p.Pro955ArgfsX95) mutation, and 11 with different, other truncating mutations.

All probands were excluded. Furthermore, the parental years lived before birth of mutation carriers were omitted to avoid “reproduction” bias, as they must have been living until this age to be able to transmit the mutation to their offspring. The small and large pedigrees were constructed out of the same pool of probands. Therefore, we excluded the small pedigrees from the large pedigrees to avoid double analyses of the same persons in the small and large pedigrees as well as to avoid referral bias in the large pedigrees. The first year of life of all individuals was omitted from our analysis, as we know that registration of neonatal mortality in the 19th century may have been incomplete.

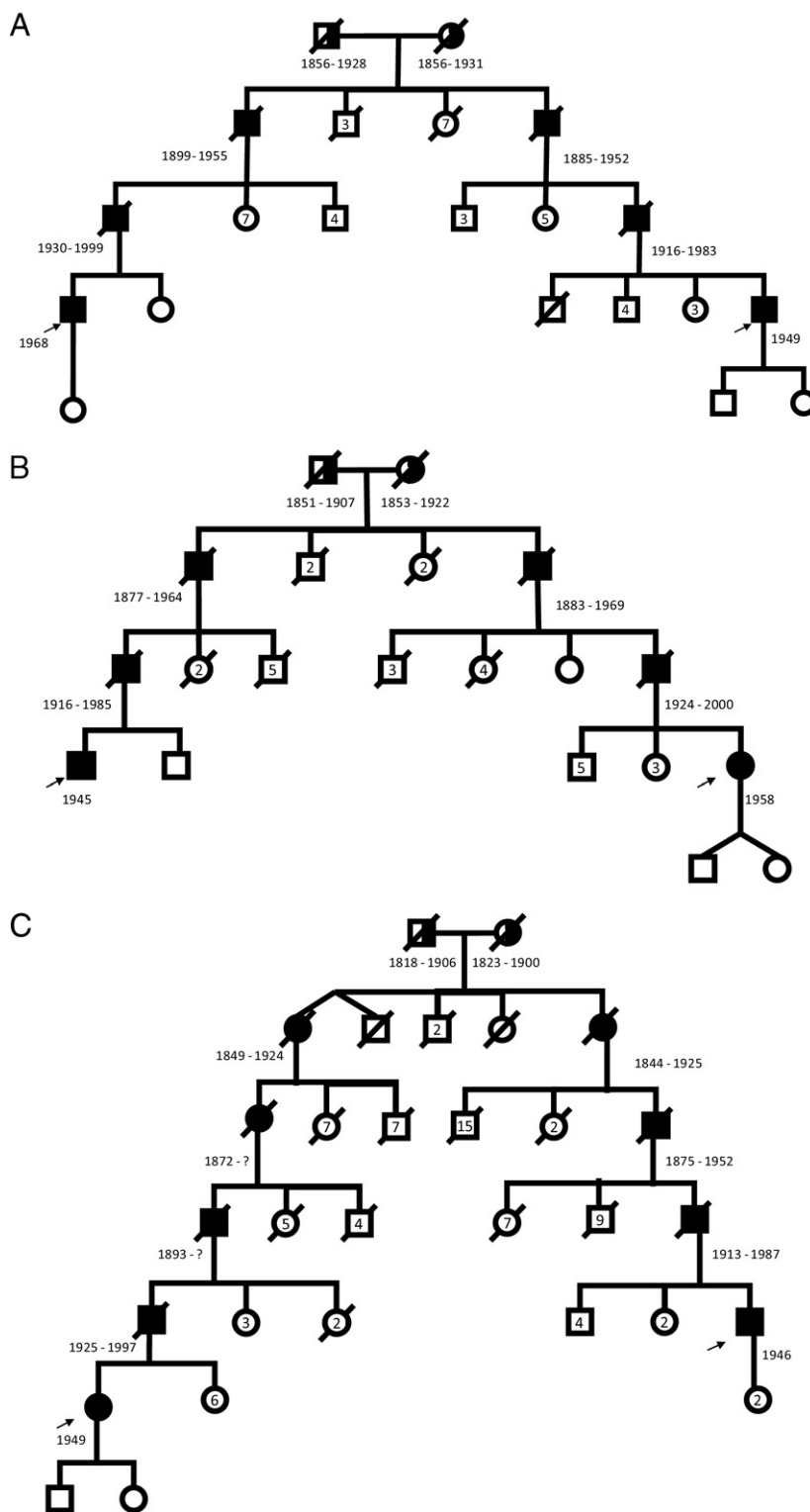
All analyses ended at death, when a diagnosis of HCM was made (and patients could have been treated for the disease) or when the mutation was identified in the family (and predictive testing became available, and treatment could have been started). Furthermore, in a subsample of the small pedigrees (62 pedigrees), we determined the cause of death under the age of 40 years and the reason for referral

### Abbreviations and Acronyms

- CI** = confidence interval
- FTMR** = family tree mortality ratio
- HCM** = hypertrophic cardiomyopathy
- MYBPC3** = myosin-binding protein C gene
- SCD** = sudden cardiac death
- SMR** = standardized mortality ratio

**Table 1** Different Truncating Mutations in the *MYBPC3* Gene

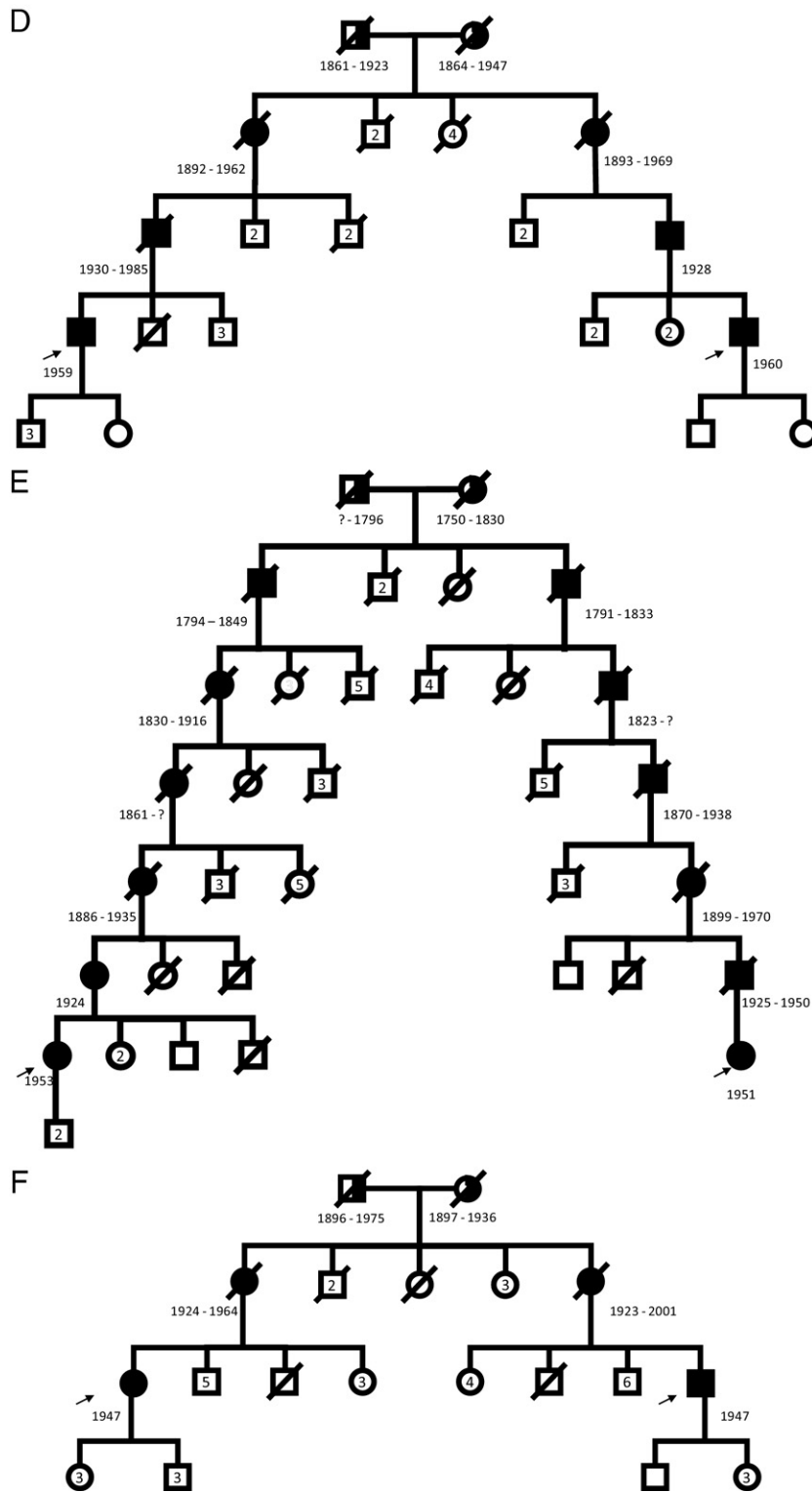
No. of Identified Mutations	Mutation <i>MYBPC3</i>	n	Type of Mutation
1	c.2373dup (p.Trp792ValfsX41)	94	Frameshift/truncating
2	c.2864–2865del(p.Pro955ArgfsX95)	11	Frameshift/truncating
3	c.2827C>T (p.Arg943X)	24	Truncating
4	c.3776del (p.Gln1259ArgfsX39)	2	Frameshift/truncating
5	c.2893C>T (p.Gln965X)	1	Truncating
6	c.3258dup (p.Lys1087GlufsX62)	1	Frameshift/truncating
7	c.932C>A (p.Ser311X)	1	Truncating
8	c.897del (p.Lys301ArgfsX49)	2	Frameshift/truncating
9	c.676–701dup (p.Gly235Serfs74X)	1	Frameshift/truncating
10	c.989del (Pro330HisfsX20)	1	Frameshift/truncating
11	c.2149–?_2737+? (p.Lys716fsX)	1	Frameshift/truncating
12	c.3181C>T (p.Gln1061X)	1	Truncating
	Total	140	



**Figure 1. Six Large Pedigrees With Carriers of the c.2373dup Mutation in the MYBPC3 Gene**

Pedigree A consists of 49 persons; pedigree B, 38 persons; and pedigree C, 92 persons.

Continued on the next page.



**Figure 1** Continued

Pedigree D consists of 34 persons; pedigree E, 60 persons; and pedigree F, 42 persons. The probands are indicated with an arrow. **Solid squares/circles** = 100% (obligate) male/female carriers; **open squares/circles** = male or female carriers with a 0.5 probability of carriership; **semi-solid squares/circles** = male or female carriers with a 0.5 probability of carriership. The crossed of subjects have passed away. *MYPBC3* = myosin-binding protein C gene.

of the proband. All probands gave informed written consent to the study.

**Statistical method (FTMR method).** The mortality in the large pedigrees and the small pedigrees (observed) was compared with the mortality of the Dutch general population (expected) standardized for age, sex, and calendar period, as described previously (29). The expected mortality was calculated by multiplying the total number of years lived by the study population with the age- and sex-specific mortality rates of the Dutch population for each calendar period available at 'Statistics Netherlands' (31). The ratio of observed to expected number of deaths is the standardized mortality ratio (SMR). The 95% confidence interval (CI) of the SMR was calculated assuming a Poisson distribution of the observed number of deaths and by using exact limits.

Cumulative survival of subgroups was performed by using Kaplan-Meier analyses and compared with Cox's regression (relative risk) using SPSS version 15.0.1 for Windows (SPSS Inc., Chicago, Illinois). A *p* value <0.05 (2-sided) was considered significant.

## Results

**Genealogical searches.** We obtained 6 large pedigrees with carriers of the c.2373dup mutation in the *MYBPC3* gene (Fig. 1). We excluded 155 persons from these pedigrees: 12 probands, 104 first-degree relatives of these 12 probands, 28 persons because of missing date of birth or death, and 11 persons who died before the age of 1 year. In total, 160 persons (92 males, 68 females) of the 6 large pedigrees were included in our analyses.

The 140 small families contained 965 first-degree relatives (siblings, parents, and offspring) with a known date of birth and death. After exclusion of the relatives who died in the first year, 958 persons were included in our analyses (508 males, 450 females).

**Mortality risk in large 200-year multigenerational pedigrees.** In the 6 pedigrees, 130 deaths occurred in 9,129 person-years between 1811 and 2002 (when the mutation was detected) among 160 individuals with a (at least) 0.5 probability of carrying the mutation. The mean SMR over that period was 0.86 (95% CI: 0.72 to 1.03), meaning that there was no overall excess mortality. However, significant excess mortality was observed in the age category of 10 to 19 years (SMR 2.7 [95% CI: 1.2 to 5.2]) (Fig. 2). We subsequently analyzed this age category through the centuries: between the periods 1804 to 1904 and 1904 to 2002, the SMR was similar: 2.8 (95% CI: 1.01 to 6.0) and 2.7 (95% CI: 0.6 to 7.8), respectively.

**Mortality risk in small (contemporary) families.** In the 140 small families, 241 deaths were observed in 37,233 person-years between 1897 and 2009 in 958 individuals with a 0.5 probability of carrying a truncating *MYBPC3* mutation. The mean SMR over this period was significantly increased (SMR 1.5 [95% CI: 1.3 to 1.6]).

The SMR was significantly increased between the ages of 10 and 19 years (SMR 2.5 [95% CI: 1.002 to 5.1]), 20 and 29 years (SMR 2.9 [95% CI: 1.5 to 5.1]), 30 and 39 years (SMR 3.8 [95% CI: 2.4 to 5.6]), and 50 and 59 years (SMR 1.9 [95% CI: 1.4 to 2.5]) (Fig. 3A). Not unexpectedly, the mortality of the c.2373dup mutation, accounting for the majority of our patients, was roughly similar to the values shown in Figure 3A (Fig. 3B).

Figure 4A reveals that survival in persons with a 0.5 probability of carrying the c.2373dup mutation in the small families was not different from carriers of other truncating *MYBPC3* mutations (log-rank test, *p* = 0.96). Females at risk of a *MYBPC3* mutation had a better survival than males (log-rank test, *p* < 0.001) (Fig. 4B). The hazard ratio for death for males relative to females with a *MYBPC3* mutation was 2.0 (95% CI: 1.5 to 2.6; *p* < 0.001) in a Cox regression model.

We determined the cause of death in those aged younger than 40 years in a subsample of the small pedigrees (62 pedigrees). SCD occurred in 13 persons (59%), 8 died of other causes (mainly motor vehicle accidents), and 1 died of an unknown cause. We looked for the reason of referral of the proband in 62 small pedigrees. Nineteen (31%) probands were referred because of HCM in the proband *and* SCD in the family. The remaining 69% were referred because of HCM only.

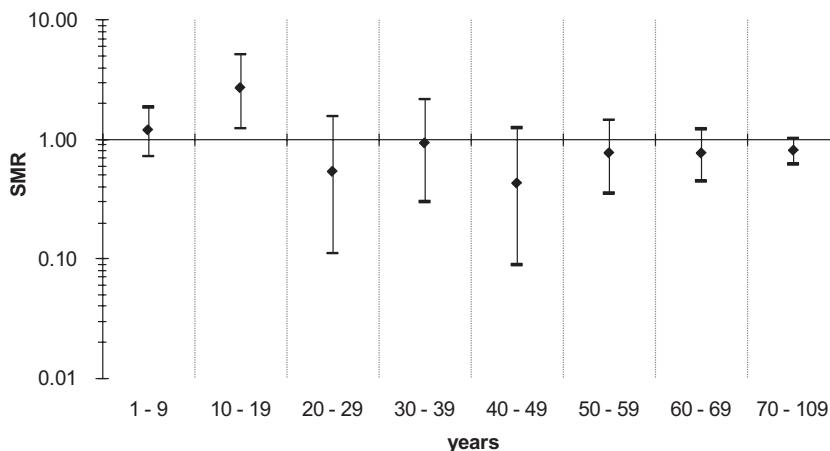
## Discussion

We studied the mortality of HCM, partly in times when the disease was not recognized and patients were not treated. The present-day physician faces an increasing need for such data on the natural history, because important decisions on screening and treatment strategies have to be made for the rapidly growing number of asymptomatic HCM mutation carriers coming to the attention of physicians.

The overall mortality in the large pedigrees was not increased. Nonetheless, we identified an age category (10 to 19 years) during which the mortality risk was significantly increased. We also studied smaller, contemporary families who were referred to our clinics because of HCM in the proband and/or familial SCD. In these families, the SMR was significantly increased from the age of 10 years until 60 years, reaching a peak between 30 and 39 years. The SMRs are based on persons with (at least) 0.5 probability of carriership; therefore, mutation carriers will have higher reported excess mortality risks.

One could argue that the difference in mortality risk between the small and the large pedigrees can be explained by differences between the calendar periods. However, this reasoning is very unlikely because the excess mortality in the large pedigrees was consistent throughout the centuries. Alternatively, the type of mutation may explain the differences in mortality risk: the large pedigrees only consisted of c.2373dup mutation carriers whereas the small pedigrees carried different *MYBPC3* mutations. However, small fam-





**Figure 2** Mortality Between 1811 and 2002 (6 Large Pedigrees) in 160 Persons With a 0.5 Probability of Carrying the c.2373dup Mutation in the *MYBPC3* Gene

The mortality according to age categories is expressed in the standardized mortality ratio (SMR) and depicted as a point estimate. 95% confidence intervals are depicted around the point estimates. *MYBPC3* = myosin-binding protein C gene.

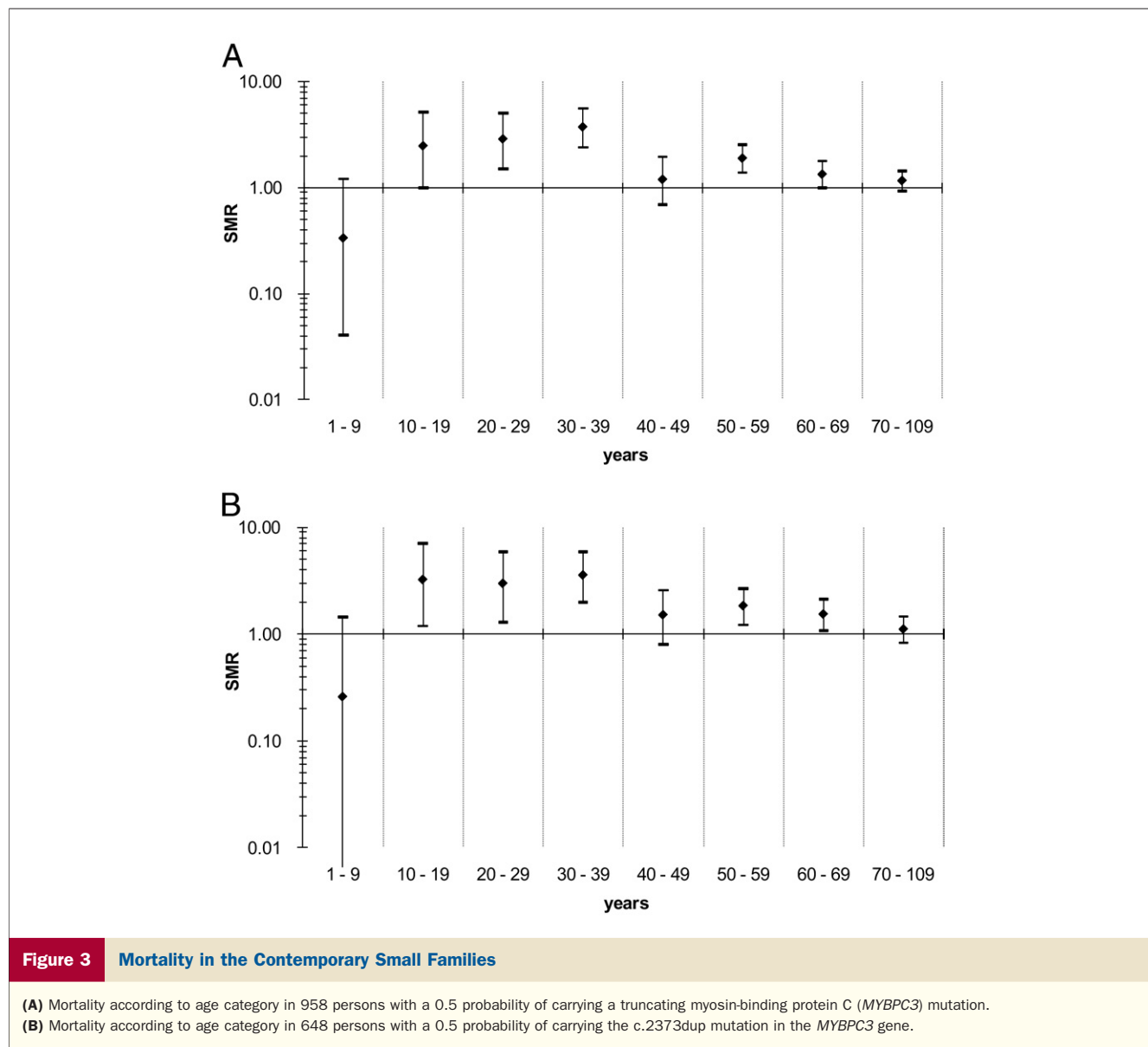
ilies with the c.2373dup mutation and families with other mutations had similar mortality risks (Figs. 3B and 4). A plausible explanation for the differences between the small and the large pedigrees is that the persons in the large HCM pedigrees were included on the basis of transmission of the mutation (based on Mendelian inheritance) and not on their severe phenotype. The probands of the small pedigrees were referred to our clinics because of manifest HCM and in 31% of cases because of a positive family history for SCD (in the first-degree relatives). The latter will certainly lead to a bias toward more severely affected persons (included in the small pedigree analyses). This finding is in line with previous HCM studies: the annual mortality rate for death for HCM in early studies was estimated at 4% to 6%, but later, larger, and more unselected studies reported lower mortality rates (approximately 1%) (27).

According to international and national HCM expert consensus, first-degree relatives of a patient with HCM are advised to seek cardiological surveillance from the age of 10 to 12 years (every 1 to 2 years until the age of 20 years; every 2 to 5 years until the age of 50 to 60 years) (3,32–34). The high mortality risks in the small families fully support this strategy of starting cardiological and genetic screening in the first-degree relatives of a proband (with a *MYBPC3* mutation) from 10 years onward (accompanied with thorough genetic counseling) until the age of 60 years. On the basis of our data, we cannot give advice about the frequency and intensity (including risk stratification) of the cardiological follow-up. The natural history of the disease is, however, best observed in the large pedigrees. Based on these results, screening of more distant relatives is probably most efficient between 10 and 19 years. Clearly, more research is required to identify the method with optimal (cost-) effectiveness.

Our finding of clear excess mortality in young age groups in both the large and small pedigrees confirm that patients with a *MYBPC3* mutation do not have a mild phenotype with a later onset of problems (19,21). We emphasize, however, that the increased mortality was certainly not limited to adolescents and young adults but extended throughout a large period of life in the small families. Although this finding confirms observations by others (26,35,36), and it will guide family screening, we would still like to improve the identification of high and low risk of SCD among *MYBPC3* mutation carriers. Therefore, future research to identify genetic modifiers and other risk factors is necessary. For instance, the present-day day high-throughput sequencing techniques may offer potential important opportunities.

In the present study, females had a better survival than males in the small families. Sex differences have been described by others; females had a more age-related disease progression, but no difference in HCM-related mortality and death from any cause was observed (37). Other studies in asymptomatic HCM mutation carriers reported males having a higher probability of a clinical diagnosis of HCM (22,23,28), and therefore possibly a higher risk of SCD. Moreover, a study in transgenic mice found that male sex aggravates the phenotype of HCM (38).

**Study limitations.** A potential limitation of our approach is that the analyses were restricted to (truncating) mutations in the *MYBPC3* gene and can therefore not be generalized to other HCM genes. However, mutations in the *MYBPC3* gene account for a large proportion of the HCM population worldwide, and most mutations in the *MYBPC3* gene are, as in our study, frameshift and nonsense truncating mutations (9). As shown in Figure 4, we observed no differences in survival between the subjects with a c.2373dup mutation



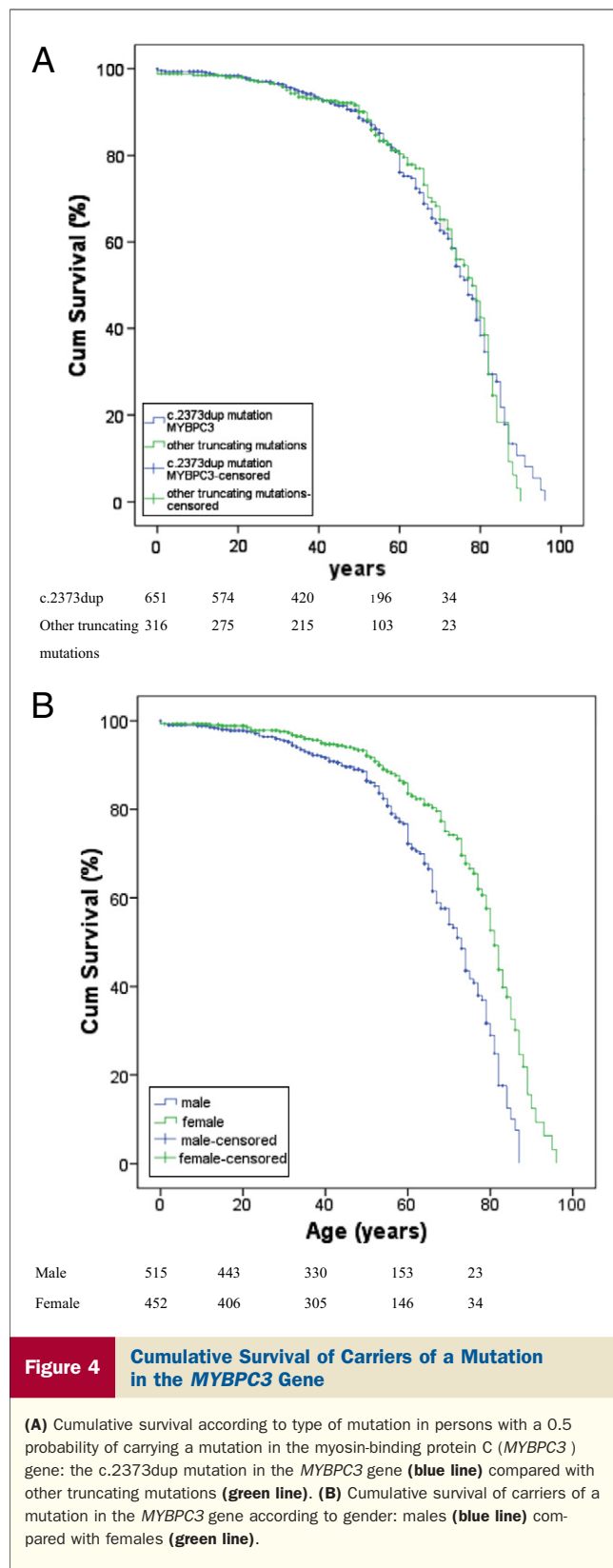
and the other truncating mutations. It is likely that these mutations share a common pathophysiological mechanism (13), and that FTMR data on one of them are potentially relevant to the vast majority of the *MYBPC3* patients and as such for approximately 30% of all patients with HCM.

For the large pedigrees, we collected data from death certificates stored at municipal archives. In these certificates, unfortunately only information about the lifespan was available, and only in a minority was the cause of death reported. The reliability of this information is poor, which is understandable: in the 19th and beginning of the 20th century the ability to make a diagnosis was difficult. Therefore, in the large pedigrees, it is not possible to retrieve exactly whether the increased mortality might have been related to the mutation in the *MYBPC3* gene. We acknowledge that this lack of information is a weakness of our study. However, from 62 small pedigrees, we determined the cause of death

in those aged younger than 40 years. SCD occurred in at least 59% of all cases. In the general population, SCD in those younger than 40 years is relatively rare (39,40), accounting for 7% of deaths in the young in one study (40). These data and data from the literature (26) indicate that SCD caused the excess mortality in the individuals in our small pedigrees under the age of 40 years and logically also caused the excess mortality in our large pedigrees.

### Conclusions

We quantified the risk for death in a large cohort of relatives of HCM patients in times when the disease was not known and patients were not treated and also in the contemporary relatives of patients referred to our outpatient clinics. With this unique way of studying the mortality of HCM, we identified age windows of high mortality risks. Our findings



support the strategy of starting cardiological and genetic screening in the first-degree relatives of a proband from 10 years onward and including persons in the screening at least until the age of 60 years. Screening of more distant relatives is probably most efficient between 10 and 19 years.

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**Key Words:** family tree mortality ratio method ■ hypertrophic cardiomyopathy ■ mortality ■ myosin-binding protein C gene ■ natural history.