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Familial Aggregation of Myocardial Infarction and Co-aggregation of Myocardial Infarction and Autoimmune Disease: a Nationwide Population-Based Cross-Sectional study in Taiwan

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3 **Familial Aggregation of Myocardial Infarction and Co-aggregation of**
4 **Myocardial Infarction and Autoimmune Disease: a Nationwide**
5 **Population-Based Cross-Sectional Study in Taiwan**
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46 **Keywords:** autoimmune disease; myocardial infarction; family history; familial
47 aggregation
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Abstract

Objective This study examined how a history of myocardial infarction (MI) in a person's first-degree relatives affects that person's risk of developing MI and autoimmune diseases.

Design Nationwide population-based cross-sectional study

Setting All healthcare facilities in Taiwan.

Participants A total of 24361345 individuals were enrolled.

Methods Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of data collected from all beneficiaries in the Taiwan National Health Insurance system in 2015, of whom 135269 had MI between 1996 and 2015. We estimated the relative risks (RRs) of MI and autoimmune disease in individuals whose first-degree relatives had a history of MI, as well as the relative contribution of genetic and environmental factors to their MI susceptibility.

Results Patients with affected first-degree relatives were significantly associated with a higher RR of MI [1.76, 95% confidence interval (CI) 1.68–1.85] compared to the general population. There was no association with a higher RR of autoimmune disease. The sibling, offspring, and parental MI history conferred RRs (95% CI) for MI of 2.35 (1.96–2.83), 2.21 (2.05–2.39), and 1.60 (1.52–1.68), respectively. The

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4 contributions of heritability, shared environmental factors, and non-shared
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6 environmental factors to MI susceptibility were 19.6%, 3.4%, and 77.0%, respectively.
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8
9 **Conclusions** Individuals who have first-degree relatives with a history of MI have a
10
11 higher risk of developing MI than the general population. Non-shared environmental
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13 factors contributed more significantly to MI susceptibility than did heritability and
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15 shared environmental factors. A family history of MI was not associated with an
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17 increased risk of autoimmune disease.
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26 **Strengths and limitations of this study**

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28
- 29 ➤ The strength of this study is the large size of the general population and the
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31 number of myocardial infarction cases allowed detailed family history analyses.
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 - 34 ➤ We used database-linked family histories of myocardial infarction, which are
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36 more reliable than self-reported family histories and have been validated.
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 - 39 ➤ We were not able to control for some important risk factors of myocardial
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41 infarction, including smoking, obesity, blood pressure, lipid levels, and physical
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43 activity.
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 - 46 ➤ The analysis of relative genetic and environmental contributions is based on the
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48 multifactorial liability model, where the results are subject to assumptions.
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INTRODUCTION

Myocardial infarction (MI) is a leading cause of death worldwide and has several risk factors including family history.¹⁻⁴ A meta-analysis of 12 case-control studies found a relative risk (RR) of 1.6 for future events in subjects with a family history of coronary heart disease (CHD).⁵ Although recall bias is a potential limitation, self-reported family history has been commonly used in previous studies.⁶⁻⁸ Family history of MI is generally available to physicians and several studies indicate that family history has been helpful in risk assessment.^{2,3,9} Two previous studies evaluated the incremental value of family history over conventional risk scores with conflicting results.^{10,11} Recent studies revealed that a detailed family history provides more information and helps stratify MI risk.^{9,12} Only a few studies have evaluated the effect of affected sex or specific type of family relationships on MI risk.^{9,12}

Atherosclerosis and autoimmune diseases share some pathogenic similarities and have a bidirectional relationship.^{13,14} Autoimmune diseases are characterized by chronic inflammation and immune dysregulation, which are characteristics also found in the development of atherosclerosis.^{14,15} These abnormalities may cause lipid peroxidation, platelet aggregation and arterial pathology.¹⁵ Therefore, patients with an autoimmune disease are more likely to develop premature and accelerated atherosclerosis than the general population.¹⁶ Given the similarities in

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4 immune-mediated inflammatory processes of the vascular system, some
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6 investigators have postulated that atherosclerosis is an immune-mediated disease.¹⁴
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9 To our knowledge, no study has yet evaluated the co-aggregation of autoimmune
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11 disease in families with a history of MI.
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15 In this retrospective cross-sectional study, we evaluate the risks of MI and
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17 autoimmune disease in individuals with a family history of MI in their first-degree
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19 relatives as well as estimate the genetic and environmental contribution to MI
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21 susceptibility.
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29 **METHODS**

30 **Study Population**

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32 The primary data source came from the National Health Insurance Research
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34 Database (NHIRD) which contains registration information and original claims data
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36 on all beneficiaries of National Health Insurance (NHI) in Taiwan since its
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38 establishment in 1995. The study population consisted of all beneficiaries enrolled in
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40 the Taiwan NHI system in 2015. We used data from the registry for beneficiaries, the
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42 registry for patients with catastrophic illness, and data sets of ambulatory care
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44 expenditures and details of ambulatory case orders. All patient records in the
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46 database are identified by their unique national identification number. To ensure
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4 confidentiality, identification numbers were encrypted before being released for
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7 research, although the uniqueness of the encrypted identification was retained to
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10 facilitate data linkage for researchers. Methods of identifying first-degree relatives
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12 and family relationship ascertainment have been reported previously.¹⁷⁻¹⁹ Briefly,
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15 linear blood relatives and spouses can be directly identified using relationship
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17
18 indicators and unique national identification numbers. Full siblings of an individual
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21 are identified through shared parents. To analyze correlations among individuals
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24 from the same family, we grouped individuals into families according to their
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27 relationships.

28 29 **Case Definitions of MI and autoimmune disease**

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32 The case definition of MI was a patient with a primary discharge diagnosis of MI as
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35 defined in the International Classification of Diseases Ninth Revision code. We only
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38 included patients' first diagnosis of MI. The diagnosis coding of MI obtained from the
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41 NHIRD has been validated with respect to its acceptable sensitivity, specificity and
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44 positive predictive value.²⁰ The case definition of autoimmune disease was a person
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47 with a catastrophic illness certification for a specific type of autoimmune diseases.
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50 The holders of a catastrophic illness certificate are entitled to a waiver for medical
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53 copayments. In order for a patient to receive a certificate for a catastrophic illness,
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56 the diagnosis must be supported by comprehensive clinical and laboratory

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4 assessments. This information is also required by the insurance administration for
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6 review by commissioned expert panels to confirm diagnosis before the waiver
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8 approval.
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11 **Covariates**

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14 Factors that may confound or modify family associations were considered, including
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16 age, sex, family size, Charlson Comorbidity Index, and socioeconomic factors (place
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18 of residence, occupation, and income level). The place of residence for each
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20 individual was categorized according to the level of urbanization, occupations were
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22 classified into five categories, and income levels were categorized into sex-specific
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24 income quintiles.
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31 **Ethics approval**

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34 This study was approved by the Institutional Review Board of Chang Gung Memorial
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36 Hospital and by the National Health Research Institutes, which compile data for the
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38 National Health Insurance Research Database (NHIRD).
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43 **Statistical analysis**

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46 We measured the prevalence of MI among individuals with affected relatives and the
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48 general population. An individual who met the case definition of MI between 1996
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50 and 2015 and had valid insurance registration in 2015 was defined as a prevalent
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52 case. The total population in Taiwan was used to calculate the prevalence of MI in
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4 2015. The RR of MI was calculated as the prevalence of MI among individuals with an
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6 affected family member divided by the prevalence of MI in the general population.
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9 We calculated the RRs for subjects with an affected first-degree relative of any
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11 kinship or an affected spouse. Because kinship and sex may influence family risk, we
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13 calculated RRs separately according to kinship and sex of affected relatives. We
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15 applied the standard ACE model to quantify the influences of additive genetic factors
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17 (A), common environmental factors (C) and non-shared environmental factors (E)
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19 accounting for individual differences in a phenotype (P).²¹ The ACE model was
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21 expressed as: $\sigma_p^2 = \sigma_A^2 + \sigma_C^2 + \sigma_E^2$, where σ_p^2 =total phenotypic variance; σ_A^2 = additive
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23 genetic variance; σ_C^2 =common environmental variance; and σ_E^2 =non-shared
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25 environmental variance. The heritability was defined as the proportion of phenotypic
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27 variance that is attributable to genetic factors and is expressed as σ_A^2/σ_p^2 and the
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29 familial transmission was expressed as $(\sigma_A^2 + \sigma_C^2)/\sigma_p^2$, which is the sum of heritability
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31 and common environmental variances. We used the polygenic liability model to
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33 calculate heritability and familial transmission.²¹⁻²⁴ The sibling RR, spouse RR, and the
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35 prevalence of MI in the general population were used to calculate the heritability and
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37 the familial transmission. The common environmental variance was calculated as the
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39 difference between familial transmission and heritability. All analyses were
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41 performed using SAS software version 9.3 (SAS Institute, Cary, NC).
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RESULTS

The study population comprised 24361345 individuals (12089044 men, 12272301 women) enrolled in the NHI system in Taiwan in 2015, of whom 135269 (33762 women and 101507 men) had MI, which is equivalent to a crude prevalence of 0.56% (0.84% in men and 0.28% in women) (table 1). From the study population, 259360 (1.06%) people had at least one first-degree relative with MI. Among these, 2255 had MI themselves (prevalence 0.87%), 1502 had affected parents, 612 had affected offspring, and 173 had affected siblings. For individuals with affected relatives, the age-specific prevalence of MI was significantly higher than in the general population (figure 1). Table 2 shows the prevalence and RR of MI in individuals with an affected first-degree relative, according to relationship and sex of affected individuals and their families. Compared with the general population, patients with an affected first-degree relative had an RR of 1.76 [95% confidence interval (CI) 1.68–1.85] for MI. Although male subjects with affected relatives showed a higher prevalence of MI than female subjects (1.25% vs. 0.34%), the RRs of MI for male (1.67, 95% CI 1.59–1.76) and female (1.74, 95% CI 1.57–1.93) subjects were similar. The RRs (95% CI) of MI were 2.35 (1.96–2.83) for those with an affected sibling, 2.21 (1.96–2.83) for those with an affected offspring, 1.60 (1.52–1.68) for those with an affected parent,

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4 1.72 (1.60–1.84) for those with an affected father, 1.53 (1.43–1.65) for those with an
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6 affected mother, and 1.15 (1.08–1.22) for those with an affected spouse. RRs of MI
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8 for those with a family history of MI in 1, 2, and 3 first-degree relatives were 1.73
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10 (1.65–1.82), 3.47 (2.66–4.51), and 14.85 (4.95–44.52), respectively.
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15 Table 3 shows the age distribution of MI cases in Taiwan in 2015, including
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17 individuals with MI in affected relatives and in the general population. In subjects
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19 with affected relatives, MI cases increased most notably from the age of 30, which
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21 was ten years earlier than the general population. Figure 2 shows that the RRs of MI
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23 in subjects with affected relatives are stratified by age. Younger individuals were
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25 associated with a higher RR of MI.
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32 Using the threshold liability model, we estimated the accountability for
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34 phenotypic variance of MI to be 19.6% for genetic factors (heritability), 3.4% for
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36 shared environmental factors, and 77.0% for non-shared environmental factors.²⁵
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38 Given previously estimated parameters, the probability of a patient having sporadic
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40 MI was 83.1%.
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46 Table 4 shows the prevalence and RRs for autoimmune diseases in individuals with
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48 first-degree relatives with MI compared with the general population. The RR (95% CI)
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50 in individuals with first-degree relatives with MI was 1.41 (1.00–2.00) for
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52 polymyositis/dermatomyositis, 1.14 (1.01–1.28) for systemic lupus erythematosus,
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4 1.05 (0.76–1.44) for inflammatory bowel disease, 0.98 (0.78–1.23) for myasthenia
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6 gravis, 0.95 (0.67–1.35) for vasculitis, 0.94 (0.59–1.48) for systemic sclerosis, 0.84
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9 (0.76–0.92) for rheumatoid arthritis, and 0.55 (0.32–0.92) for Behçet disease.
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14 **DISCUSSION**

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17 In this study, we evaluated the familial aggregation of MI and co-aggregation of
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19 autoimmune disease and MI in a population of more than 24 million. This analysis
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21 yielded five main findings: First, patients with at least one affected first-degree
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23 relative were 1.76-fold more likely to suffer from MI than the general population.
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26 The sibling, offspring, parental, paternal and maternal history of MI conferred RRs of
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28 MI of 2.35, 2.21, 1.60, 1.72, and 1.53, respectively. Second, for individuals with
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30 first-degree relatives with MI, MI events occurred ten years earlier than for the
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32 general population, and younger individuals were associated with a higher RR of MI.
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35 Third, the more frequently MI occurred in an individual's first-degree relatives, the
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37 higher that individual's risk of MI. Fourth, shared environmental and genetic variance
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39 played only a minor role in MI susceptibility, but non-shared environmental factors
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41 accounted for more than three-quarters of the phenotypic variance in MI. Finally, a
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43 family history of MI in first-degree relatives was not associated with an increased risk
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46 for a majority of most of autoimmune diseases.
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4 The increased MI risk associated with family history found in our study aligns with
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6 results of previous case-controlled and population-based studies.^{3 5 7 9 10 12} A
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8 meta-analysis of 12 case-control studies yielded an RR of 1.60 (95% CI 1.44–1.77) for
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10 CHD in individuals with an affected relative,⁵ which is similar to our estimate of 1.76
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12 (95% CI 1.68–1.85) for subjects with affected first-degree relatives. The RRs
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14 estimated in some studies were greater than ours, however.^{7 12} For instance, a
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16 nationwide population study in Denmark found high MI risks in subjects with an
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18 affected sibling (RR 4.3, 95% CI 3.53–5.23) or mother (RR 2.4, 95% CI 2.20–2.60),¹²
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20 which is higher than our findings for these relationships (RR 2.35, 95% CI 1.96–2.83
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22 and RR 1.59, 95% CI 1.48–1.70, respectively). The Danish study only included persons
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24 younger than 58 years of age, which is a younger study population than the present
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26 study. Another case-control study, of women aged 18–44 years, also found a higher
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28 MI risk in subjects with affected siblings.²⁶ In the present study, we found that a
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30 family history of MI in first-degree relatives was associated with a higher RR of MI in
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32 younger subjects (figure 2). The more frequently MI occurred in an individual's
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34 first-degree relatives, the higher that individual's risk of MI. Similar findings were also
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36 observed in another Danish population study, which found that a history of MI in
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38 second-degree relatives was also associated with an increased risk of MI.⁹
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54 Although familial aggregation of MI has been shown repeatedly in previous
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4 studies,^{1 7 12} it still has not been determined whether such aggregation is largely
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6 related to shared genes or environmental factors. Assuming spouses share similar
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8 familial environments but not genetics with other family members, they can be used
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10 to estimate the relative contribution of shared environmental factors to MI
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12 susceptibility.²¹⁻²⁴ We found that shared environmental factors contributed minimally,
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14 only around 20% of phenotypic variance of MI was related to genetics. Non-shared
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16 environmental factors accounted for more than three-quarters of the phenotypic
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18 variance of MI. Compared to 43.9% of the genetic contribution of phenotypic
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20 variance in systemic lupus erythematosus,¹⁹ genetic variance in MI heritability can be
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22 regarded as a minor component.¹⁹ Given that multiple risk factors of MI such as
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24 hyperlipidemia, hypertension, and diabetes mellitus have substantial heritability,²⁷⁻²⁹
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26 the genetic contribution of MI may be even lower.
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37 It is still debatable whether autoimmunity plays an essential role in the
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39 development of atherosclerosis,¹⁴ which is the underlying cause of MI in most
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41 cases.³⁰ Patients with autoimmune diseases are at an increased risk of suffering
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43 accelerated atherosclerosis and premature MI.^{31 32} Despite findings in previous
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45 studies suggesting that autoimmune diseases share part of the pathogenesis of
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47 atherosclerosis,^{13 33} the extent and contributions to disease manifestation may differ.
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54 Atherosclerosis starts with endothelial injury followed by subendothelial
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4 accumulation of low-density lipoproteins, which triggers macrophages and type one
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6 T helper cells to form atherosclerotic plaques.^{34 35} Inflammation is initiated by the
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8 innate immune system oxidizing low-density lipoproteins and is perpetuated by type
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10 one T helper cells that react to autoantigens from the apolipoprotein B100 in
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12 low-density lipoproteins.³⁵ Chronic inflammation activated by the innate immune
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14 system is responsible for most atherosclerosis development, in which autoimmunity
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16 only plays a minor role. In the present study, we found that there was no
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18 co-aggregation of autoimmune disease in families affected by MI. Our results support
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20 the notion that atherosclerosis should be regarded as a chronic inflammatory disease
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22 rather than an autoimmune disease.
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32 Our results have several implications. First, the study provides quantitative
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34 estimates of absolute risks and RRs, familial transmission, and the proportion of
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36 sporadic cases of MI. These estimates are valuable in clinical counseling. Compared
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38 to the general population, younger subjects with first-degree relatives with MI were
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40 at a higher risk of developing MI in the future. The absence of co-aggregation
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42 between MI and autoimmune diseases suggests that further evaluation of different
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44 pathogenic mechanisms is required.
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52 The size of the cohort and the number of MI cases allowed detailed family history
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54 analyses and contribute to the strength of this study. Additionally, instead of using
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4 self-reported family histories of MI, we used database-linked family histories, which
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6 are more reliable and have been validated. Moreover, self-reported measures of
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8 family history in previous studies often included multiple events (CHD, stroke, death)
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10 or cases with varying severity (stable angina, unstable angina, MI).⁶³⁶ By comparison,
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12 we used only the primary discharge diagnosis of MI, which is a strict and validated
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14 endpoint that is subject to less misclassification and yields more interpretable
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16 estimates.
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26 **Limitations**

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28 Some limitations of the present study should be acknowledged. First, this study was
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30 confined to Taiwan. Although it covered the entire population of Taiwan, the results
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32 may not be generalized and applied to other settings. Second, the NHIRD is primarily
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34 a health insurance database that contains only limited information on clinical
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36 diagnosis criteria. We did not have access to all information concerning traditional MI
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38 risk factors, including smoking, obesity, index, blood pressure, lipid levels, and
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40 physical activity. Third, the analysis of relative genetic and environmental
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42 contributions should be interpreted with caution because it is based on the
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44 multifactorial liability model, where the results are subject to assumptions. However,
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46 published data on other diseases, such as schizophrenia and systemic lupus
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3 erythematosus support the validity of this model.^{19 37} Finally, we cannot account for
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6 the effects of assortative mating, whereby spouses are more phenotypically similar
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9 than if mating were to occur at random in a population.
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11 12 13 14 15 **CONCLUSION**

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17 In this population-based cohort study, MI was found to aggregate in families, and
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19 non-shared environmental factors seemed to contribute more to the phenotypic
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21 variance of MI than genetic factors. There was no co-aggregation of autoimmune
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23 disease in families affected by MI.
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33
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35
36 monitoring, analyzing and interpreting the data. Part of data was obtained via
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39
40 Administration.
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46 **Contributors** Concept of study: C-F K and S-H C. Study design: C-L W, C-F K, Y-H Y,
47
48 M-Y H, and S-H C. Statistical analysis: C-L W and M-Y H. Interpretation of results: C-L
49
50 W, M-Y H, and S-H C. Manuscript writing: C-L W and S-H C. The other authors
51
52 provided inputs, expertise, and critical review of the manuscript.
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5
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7

8
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11 those of National Health Insurance Administration, Department of Health or National
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13 Health Research Institutes.
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17 **Competing interests** None declared.
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19
20 **Patient consent** Not required.
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23 **Ethics approval** This study was approved by the Institutional Review Board of Chang
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25 Gung Memorial Hospital and by the National Health Research Institutes, which
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27 compile data for the National Health Insurance Research Database.
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31 **Data sharing statement** Extra data are available by emailing the corresponding
32
33 author (afen.chang@gmail.com).
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Table 1 Baseline characteristics of individuals with affected first-degree relatives with myocardial infarction and the general population

	Women			Men		
	≥1 affected Relatives	General population	P value	≥1 affected Relatives	General population	P value
No. of subjects	109371	12272301		149989	12089044	
Age (y), mean (SD)	40.3 (21.0)	39.6 (16.8)	<0.0001	38.9 (20.9)	41.7 (15.6)	<0.0001
MI (%)	376 (0.3)	33 762 (0.3)	<0.0001	1 879 (1.3)	101 507 (0.8)	<0.0001
Place of residence (%)			<0.0001			<0.0001
Urban	76254 (69.7)	7740136 (63.1)		99079 (66.1)	7309940 (60.5)	
Suburban	28195 (25.8)	3624603 (29.5)		43568 (29.1)	3848868 (31.8)	
Rural	4733 (4.3)	872384 (7.11)		7086 (4.7)	895750 (7.4)	

Unknown	189 (0.2)	35178 (0.3)	256 (0.17)	34486 (0.3)
Income levels (%)			<0.0001	<0.0001
Quintile 1	18783(17.2)	2062900(16.8)	29225 (19.5)	2310684 (19.1)
Quintile 2	15135 (13.8)	1838185(15.0)	15425(10.3)	1506475 (12.5)
Quintile 3	27496 (25.1)	3658895 (29.8)	34394 (22.9)	3207226 (26.5)
Quintile 4	24975 (22.8)	2411506 (19.7)	30457 (20.3)	2241214 (18.5)
Quintile 5	22962 (21.0)	2298595 (18.7)	40466 (27.0)	2821626 (23.3)
Unknown	20 (0.0)	2220 (0.0)	22 (0.0)	1819 (0.0)
Occupation (%)			<0.0001	<0.0001
Dependents of the insured individuals	26186 (23.9)	4535168(37.0)	26276 (17.5)	3746793 (31.0)

Civil servants, teachers, military

personnel and veterans 5481 (5.0) 343851 (2.8) 9 641(6.3) 570 840 (4.7)

Non-manual workers and

professionals 44 824 (41.0) 3642834 (29.7) 61 947 (41.3) 3934252 (32.5)

Manual workers 20894 (19.1) 2609974 (21.3) 30635 (20.4) 2286403 (18.9)

Other 11986 (11.0) 1140474 (9.3) 21490 (14.3) 1550756 (12.8)

Table 2 Relative risks for myocardial infarction in patients with myocardial infarction in first-degree relatives

Type of affected relative	Sex of affected relative	Sex of individual	No. of cases	Prevalence (%)	Relative risk (95% CI)*
Any	Male	Male	1 198	1.08	1.84 (1.72–1.96)
		Female	307	0.35	1.76 (1.58–1.97)
		All	1 505	0.76	1.92 (1.81–2.03)
	Female	Male	739	1.84	1.52 (1.41–1.63)
		Female	73	0.32	1.69 (1.27–2.25)
		All	812	1.30	1.59 (1.48–1.70)
	All	Male	1 879	1.25	1.67 (1.59–1.76)
		Female	376	0.34	1.74 (1.57–1.93)
		All	2 255	0.87	1.76 (1.68–1.85)
Parent	Male	Male	756	0.74	1.67 (1.55–1.79)
		Female	40	0.05	1.21 (0.89–1.64)
		All	796	0.45	1.72 (1.60–1.84)
	Female	Male	706	1.80	1.50 (1.39–1.61)
		Female	43	0.20	1.25 (0.93–1.69)
		All	749	1.23	1.53 (1.43–1.65)

	All	Male	1 421	1.01	1.56 (1.48–1.64)
		Female	81	0.08	1.22 (0.98–1.51)
		All	1 502	0.63	1.60 (1.52–1.68)
Offspring	Male	Male	302	8.02	2.15 (1.93–2.40)
		Female	260	3.34	1.95 (1.73–2.19)
		All	562	4.87	2.18 (2.01–2.36)
	Female	Male	26	7.60	2.40 (1.66–3.45)
		Female	28	4.75	3.31 (2.32–4.72)
		All	54	5.79	2.94 (2.27–3.80)
	All	Male	326	7.94	2.16 (1.95–2.40)
		Female	286	3.42	2.01 (1.80–2.25)
		All	612	4.91	2.21 (2.05–2.39)
Sibling	Male	Male	154	2.95	2.48 (2.04–3.01)
		Female	9	0.23	1.20 (0.62–2.30)
		All	163	1.77	2.40 (1.99–2.90)
	Female	Male	8	1.49	1.48 (0.74–.98)
		Female	1	0.60	5.24 (0.77–35.54)
		All	10	1.15	1.75 (0.88–3.46)
	All	Male	162	2.81	2.40 (1.99–2.89)

Female	11	0.25	1.40 (0.74–2.65)
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All	173	1.72	2.35 (1.96–2.83)
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*Adjusted for age, gender, place of residence, quintiles of income levels, occupation and family size. CI, confidence interval.

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Table 3 Age-specific prevalence of myocardial infarction in individuals with a first-degree relative with MI and the general population in Taiwan in 2015

Age, y	First-degree relative with MI			General population		
	Case	Population	Prevalence, %	Case	Population	Prevalence, %
0-4	0	1198	0.00	4	1051252	0.00
5-9	0	2671	0.00	4	974384	0.00
10-14	0	5835	0.00	13	1153257	0.00
15-19	0	11300	0.00	37	1505997	0.00
20-24	1	17328	0.01	75	1748236	0.00
25-29	7	23469	0.03	179	1784709	0.01
30-34	40	37278	0.11	595	2095030	0.03
35-39	88	37707	0.23	1788	2157768	0.08
40-44	105	22745	0.46	3539	1853362	0.19
45-49	198	22939	0.86	6550	1865602	0.35
50-54	292	23093	1.26	10845	1877518	0.58
55-59	320	19940	1.60	14980	1737170	0.86
60-64	357	14554	2.48	18926	1521260	1.24
65-69	235	7453	3.15	17146	982469	1.75

70-74	166	4041	4.11	15303	685355	2.23
75-79	161	3214	5.01	15542	578084	2.69
80-84	139	2235	6.22	13827	407735	3.39
85-89	97	1507	6.44	10510	258837	4.06
≥90	49	847	5.79	5406	123320	4.38

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Table 4 Relative risks (RRs) of autoimmune diseases in subjects with myocardial infarction in first-degree relatives

Autoimmune diseases	Sex	Subjects with MI in first-degree relatives		General population		RR (95% CI)*
		No.	Prevalence, %	No.	Prevalence, %	
Congenital hypothyroidism	Male	27	0.02	4347	0.04	0.95 (0.65–1.38)
	Female	54	0.05	6575	0.05	0.90 (0.69–1.18)
	All	81	0.03	10922	0.04	0.89 (0.71–1.10)
Rheumatoid arthritis	Male	114	0.08	11163	0.09	0.83 (0.69–1.00)
	Female	284	0.26	44686	0.36	0.85 (0.76–0.96)
	All	398	0.15	55849	0.23	0.84 (0.76–0.92)
Sjögren's syndrome	Male	32	0.02	2359	0.02	1.01 (0.70–1.46)
	Female	242	0.22	19315	0.16	1.08 (0.94–1.26)

	All	274	0.11	21674	0.09	1.06 (0.93–1.21)
Systemic lupus erythematosus	Male	28	0.02	2209	0.02	0.91 (0.64–1.29)
	Female	178	0.16	20552	0.17	1.18 (1.04–1.34)
	All	206	0.08	22761	0.09	1.14 (1.01–1.28)
Systemic sclerosis	Male	7	0.00	461	0.00	1.06 (0.51–2.22)
	Female	11	0.01	1615	0.01	0.88 (0.49–1.57)
	All	18	0.01	2076	0.01	0.94 (0.59–1.48)
Polymyositis /Dermatomyositis	Male	9	0.01	646	0.01	0.98 (0.51–1.87)
	Female	22	0.02	1472	0.01	1.74 (1.15–2.62)
	All	31	0.01	2118	0.01	1.41 (1.00–2.00)
Behçet disease	Male	7	0.00	883	0.01	0.53 (0.25–1.12)
	Female	7	0.01	1186	0.01	0.58 (0.28–1.21)

	All	14	0.01	2069	0.01	0.55 (0.32–0.92)
Vasculitis	Male	23	0.02	3087	0.03	1.07 (0.71–1.60)
	Female	10	0.01	1958	0.02	0.79 (0.43–1.47)
	All	33	0.01	5045	0.02	0.95 (0.67–1.35)
Inflammatory bowel disease	Male	32	0.02	1798	0.01	1.21 (0.86–1.70)
	Female	5	0.00	1009	0.01	0.56 (0.23–1.34)
	All	37	0.01	2807	0.01	1.05 (0.76–1.44)
Multiple sclerosis	Male	0	0.00	354	0.00	0.18 (0.03–1.27)
	Female	12	0.01	1234	0.01	0.97 (0.56–1.71)
	All	13	0.01	1588	0.01	0.73 (0.42–1.25)
Myasthenia gravis	Male	41	0.03	2820	0.02	1.11 (0.82–1.50)
	Female	34	0.03	4312	0.04	0.87 (0.62–1.21)

	All	75	0.03	7132	0.03	0.98 (0.78–1.23)
Type 1 diabetes mellitus	Male	86	0.06	4884	0.04	0.96 (0.78–1.18)
	Female	91	0.08	5841	0.05	0.99 (0.82–1.21)
	All	177	0.07	10725	0.04	0.98 (0.85–1.13)

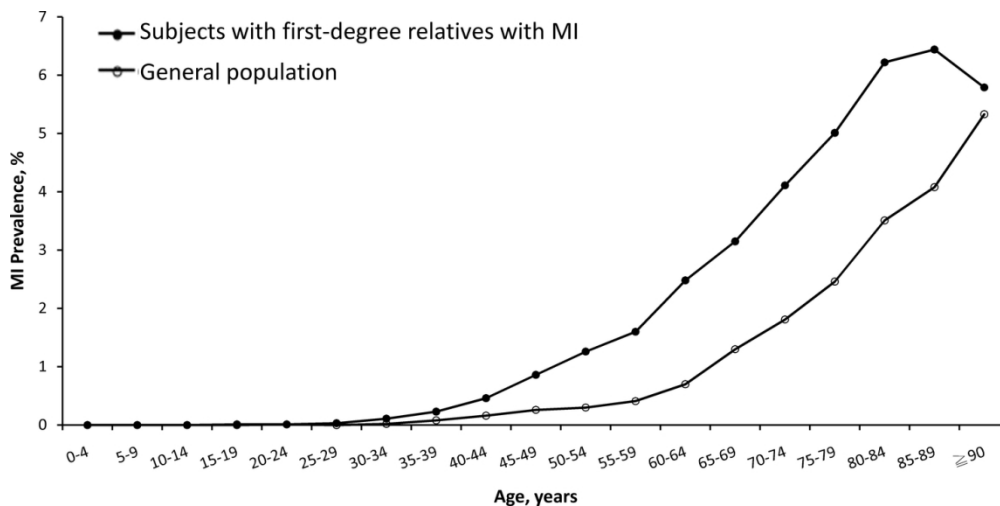
*Adjusted for age, gender, place of residence, quintiles of income levels, occupation, family size and Charlson comorbidity index.

Figure Legends

Figure 1. Age-specific prevalence of myocardial infarction (MI) in subjects with MI in first-degree relatives and in the general population in Taiwan in 2015.

Figure 2. The relative risk of MI in subjects with affected first-degree relatives stratified by the age of the evaluated subjects compared to the general population.

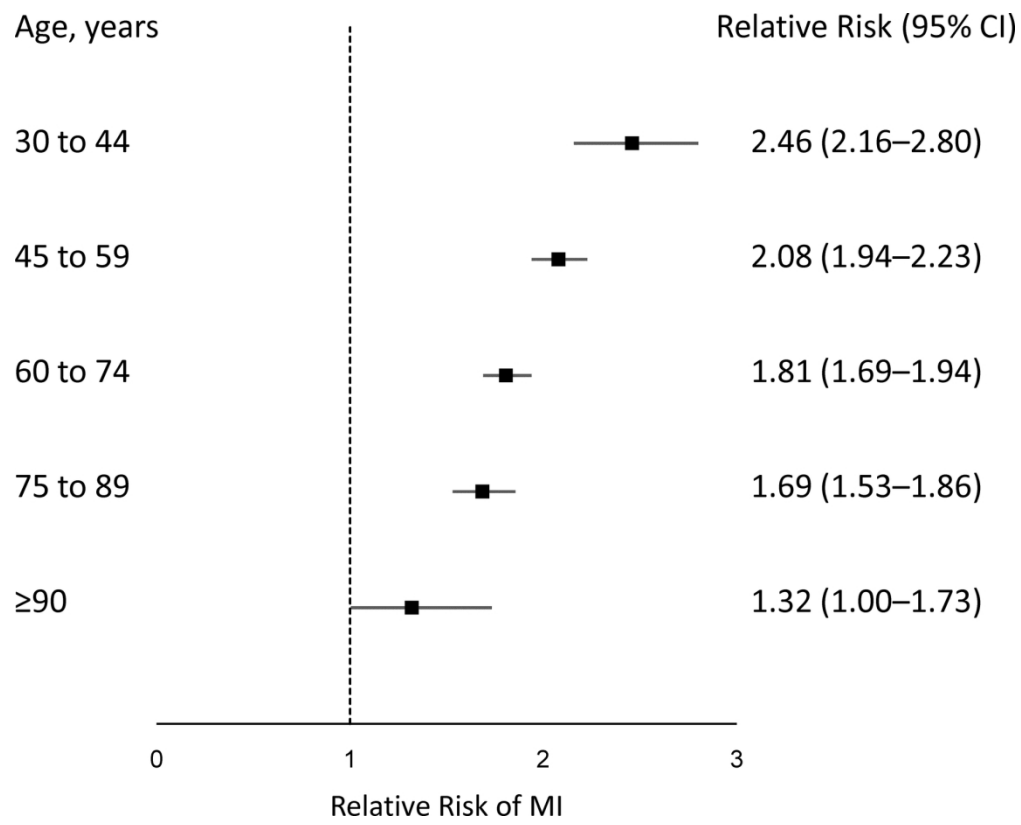
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Age-specific prevalence of myocardial infarction (MI) in subjects with MI in first-degree relatives and in the general population in Taiwan in 2015.

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The relative risk of MI in subjects with affected first-degree relatives stratified by the age of the evaluated subjects compared to the general population.

162x130mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Page 5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 5-6
Bias	9	Describe any efforts to address potential sources of bias	Page 6
Study size	10	Explain how the study size was arrived at	Pages 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Pages 7-8
		(b) Describe any methods used to examine subgroups and interactions	Pages 7-8
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	Pages 7-8

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9
		(b) Give reasons for non-participation at each stage	Page 9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 9
		(b) Indicate number of participants with missing data for each variable of interest	Page 9
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Pages 9-11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 9-11
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Familial Aggregation of Myocardial Infarction and Co-aggregation of Myocardial Infarction and Autoimmune Disease: a Nationwide Population-Based Cross-Sectional study in Taiwan

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Manuscripts

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4 **Familial Aggregation of Myocardial Infarction and Co-aggregation of**
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6 **Myocardial Infarction and Autoimmune Disease: a Nationwide**
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9 **Population-Based Cross-Sectional Study in Taiwan**
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54 **Keywords:** autoimmune disease; myocardial infarction; family history; familial aggregation

Abstract

Objective This study examined how a history of myocardial infarction (MI) in a person's first-degree relatives affects that person's risk of developing MI and autoimmune diseases.

Design Nationwide population-based cross-sectional study

Setting All healthcare facilities in Taiwan.

Participants A total of 24361345 individuals were enrolled.

Methods Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of data collected from all beneficiaries in the Taiwan National Health Insurance system in 2015, of whom 259360 subjects had at least one first-degree relative affected by MI in 2015. We estimated the absolute risks and relative risks (RRs) of MI and autoimmune disease in those subjects, and the relative contribution of genetic and environmental factors to their MI susceptibility.

Results The absolute risks of MI for subjects with at least one affected first-degree relative and general population were 0.87% and 0.56% in 2015. Patients with affected first-degree relatives were significantly associated with a higher RR of MI [1.76, 95% confidence interval (CI) 1.68–1.85] compared to the general population. There was no association with a higher RR of autoimmune disease. The sibling, offspring, and parental MI history conferred RRs (95% CI) for MI of 2.35 (1.96–2.83), 2.21 (2.05–2.39), and 1.60 (1.52–1.68), respectively. The contributions of heritability, shared environmental factors, and non-shared environmental

factors to MI susceptibility were 19.6%, 3.4%, and 77.0%, respectively.

Conclusions Individuals who have first-degree relatives with a history of MI have a higher risk of developing MI than the general population. Non-shared environmental factors contributed more significantly to MI susceptibility than did heritability and shared environmental factors. A family history of MI was not associated with an increased risk of autoimmune disease.

Strengths and limitations of this study

- This study provides quantitative estimates of relative risks of developing myocardial infarction and autoimmune disease in individuals with a family history of myocardial infarction.
- The strength of this study is the large size of the general population and the number of myocardial infarction cases allowed detailed family history analyses.
- We used database-linked family histories of myocardial infarction, which are more reliable than self-reported family histories and have been validated.
- We were not able to control for some important risk factors of myocardial infarction, including smoking, obesity, blood pressure, lipid levels, and physical activity.
- The analysis of relative genetic and environmental contributions is based on the multifactorial liability model, where the results are subject to assumptions.

INTRODUCTION

Myocardial infarction (MI) is a leading cause of death worldwide and has several risk factors including family history.¹⁻⁴ A meta-analysis of 12 case-control studies found a relative risk (RR) of 1.6 for future events in subjects with a family history of coronary heart disease (CHD).⁵ Although recall bias is a potential limitation, self-reported family history has been commonly used in previous studies.⁶⁻⁸ Family history of MI is generally available to physicians and several studies indicate that family history has been helpful in risk assessment.^{2 3 9} Two previous studies evaluated the incremental value of family history over conventional risk scores with conflicting results.^{10 11} Recent studies revealed that a detailed family history provides more information and helps stratify MI risk.^{9 12} Only a few studies have evaluated the effect of affected sex or specific type of family relationships on MI risk.^{9 12}

Atherosclerosis and autoimmune diseases share some pathogenic similarities and have a bidirectional relationship.^{13 14} Autoimmune diseases are characterized by chronic inflammation and immune dysregulation, which are characteristics also found in the development of atherosclerosis.^{14 15} These abnormalities may cause lipid peroxidation, platelet aggregation and arterial pathology.¹⁵ Therefore, patients with an autoimmune disease are more likely to develop premature and accelerated atherosclerosis than the general population.¹⁶ Given the similarities in immune-mediated inflammatory processes of the vascular system, some investigators have postulated that atherosclerosis is an

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3 immune-mediated disease.¹⁴ To our knowledge, no study has yet evaluated the
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6 co-aggregation of autoimmune disease in families with a history of MI.
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9 In this retrospective cross-sectional study, we evaluate the risks of MI and autoimmune
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12 disease in individuals with a family history of MI in their first-degree relatives as well as
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15 estimate the genetic and environmental contribution to MI susceptibility.
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20 **METHODS**

21 **Study Population**

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26 The primary data source came from the National Health Insurance Research Database
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28 (NHIRD) which contains registration information and original claims data on all beneficiaries
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31 of National Health Insurance (NHI) in Taiwan since its establishment in 1995. The study
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34 population consisted of all beneficiaries enrolled in the Taiwan NHI system in 2015. We used
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37 data from the registry for beneficiaries, the registry for patients with catastrophic illness, and
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40 data sets of ambulatory care expenditures and details of ambulatory case orders. All patient
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43 records in the database are identified by their unique national identification number. To
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46 ensure confidentiality, identification numbers were encrypted before being released for
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49 research, although the uniqueness of the encrypted identification was retained to facilitate
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52 data linkage for researchers. Methods of identifying first-degree relatives and family
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55 relationship ascertainment have been reported previously.¹⁷⁻¹⁹ Briefly, linear blood relatives
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4 and spouses can be directly identified using relationship indicators and unique national
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6 identification numbers. Full siblings of an individual are identified through shared parents.
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9 To analyze correlations among individuals from the same family, we grouped individuals into
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11 families according to their relationships.
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18 **Patient and public involvement**

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20 This is a database study using the Taiwan National Health Insurance Research Database. No
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22 patients or public were involved in developing the research question or outcome measures.
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26 No patients were involved in the design for this study. The results of the research were not
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28 disseminated to those study subjects. No patients or public were asked to advise on the
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30 interpretation or the writing up of the results.
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38 **Case Definitions of MI and autoimmune disease**

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41 The case definition of MI was a patient with a primary discharge diagnosis of MI as defined
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43 in the International Classification of Diseases Ninth Revision code. We only included patients'
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45 first diagnosis of MI. The diagnosis coding of MI obtained from the NHIRD has been
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47 validated with respect to its acceptable sensitivity, specificity and positive predictive value.²⁰
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52 The case definition of autoimmune disease was a person with a catastrophic illness
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54 certification for a specific type of autoimmune diseases. The holders of a catastrophic illness
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4 certificate are entitled to a waiver for medical copayments. In order for a patient to receive a
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6 certificate for a catastrophic illness, the diagnosis must be supported by comprehensive
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8 clinical and laboratory assessments. This information is also required by the insurance
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10 administration for review by commissioned expert panels to confirm diagnosis before the
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12 waiver approval.
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16 17 **Covariates**

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19 Factors that may confound or modify family associations were adjusted, including age, sex,
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21 family size, Charlson Comorbidity Index, and socioeconomic factors (place of residence,
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23 occupation, and income level). The place of residence for each individual was categorized
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25 according to the level of urbanization, occupations were classified into five categories, and
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27 income levels were categorized into sex-specific income quintiles.
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34 35 **Ethics approval**

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37 This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital
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39 and by the National Health Research Institutes, which compile data for the National Health
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41 Insurance Research Database (NHIRD).
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46 47 **Statistical analysis**

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49 We measured the prevalence of MI among individuals with affected relatives and the
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51 general population. An individual who met the case definition of MI between 1996 and 2015
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53 and had valid insurance registration in 2015 was defined as a prevalent case. The total
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4 population in Taiwan was used to calculate the absolute risk of MI in 2015. The RR of MI was
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6 calculated as the cases of MI among individuals with an affected family member divided by
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8 the cases of MI in the general population. We calculated the RRs for subjects with an
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10 affected first-degree relative of any kinship or an affected spouse. Because kinship and sex
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12 may influence family risk, we calculated RRs separately according to kinship and sex of
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14 affected relatives. We applied the standard ACE model to quantify the influences of additive
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16 genetic factors (A), common environmental factors (C) and non-shared environmental
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18 factors (E) accounting for individual differences in a phenotype (P).²¹ The ACE model was
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20 expressed as: $\sigma_p^2 = \sigma_A^2 + \sigma_C^2 + \sigma_E^2$, where σ_p^2 =total phenotypic variance; σ_A^2 = additive
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22 genetic variance; σ_C^2 =common environmental variance; and σ_E^2 =non-shared environmental
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24 variance. The heritability was defined as the proportion of phenotypic variance that is
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26 attributable to genetic factors and is expressed as σ_A^2/σ_p^2 and the familial transmission was
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28 expressed as $(\sigma_A^2 + \sigma_C^2)/\sigma_p^2$, which is the sum of heritability and common environmental
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30 variances. We used the polygenic liability model to calculate heritability and familial
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32 transmission.²¹⁻²⁴ The sibling RR, spouse RR, and the cases of MI in the general population
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34 were used to calculate the heritability and the familial transmission. The common
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36 environmental variance was calculated as the difference between familial transmission and
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38 heritability. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary,
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RESULTS

The study population comprised 24361345 individuals (12089044 men, 12272301 women) enrolled in the NHI system in Taiwan in 2015, of whom 135269 (33762 women and 101507 men) had MI, which is equivalent to an absolute risk of 0.56% (0.84% in men and 0.28% in women) (table 1). From the study population, 259360 (1.06%) people had at least one first-degree relative with MI. Among these, 2255 had MI themselves (absolute risk 0.87%), 1502 had affected parents, 612 had affected offspring, and 173 had affected siblings. For individuals with affected relatives, the age-specific prevalence of MI was significantly higher than in the general population (figure 1). Table 2 shows the absolute risk and RR of MI in individuals with an affected first-degree relative, according to relationship and sex of affected individuals and their families. Compared with the general population, patients with an affected first-degree relative had an RR of 1.76 [95% confidence interval (CI) 1.68–1.85] for MI. Although male subjects with affected relatives showed a higher prevalence of MI than female subjects (1.25% vs. 0.34%), the RRs of MI for male (1.67, 95% CI 1.59–1.76) and female (1.74, 95% CI 1.57–1.93) subjects were similar. The RRs (95% CI) of MI were 2.35 (1.96–2.83) for those with an affected sibling, 2.21 (1.96–2.83) for those with an affected offspring, 1.60 (1.52–1.68) for those with an affected parent, 1.72 (1.60–1.84) for those with an affected father, 1.53 (1.43–1.65) for those with an affected mother, and 1.15 (1.08–1.22)

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4 for those with an affected spouse. RRs of MI for those with a family history of MI in 1, 2, and
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6 3 first-degree relatives were 1.73 (1.65–1.82), 3.47 (2.66–4.51), and 14.85 (4.95–44.52),
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9 respectively.

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12 Table 3 shows the age distribution of MI cases in Taiwan in 2015, including individuals
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14 with MI in affected relatives and in the general population. In subjects with affected relatives,
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17 MI cases increased most notably from the age of 30, which was ten years earlier than the
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20 general population. Figure 2 shows that the RRs of MI in subjects with affected relatives are
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23 stratified by age. Younger individuals were associated with a higher RR of MI.
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27 Using the threshold liability model, we estimated the accountability for phenotypic
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29 variance of MI to be 19.6% for genetic factors (heritability), 3.4% for shared environmental
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31 factors, and 77.0% for non-shared environmental factors.²⁵ Given previously estimated
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34 parameters, the probability of a patient having sporadic MI was 83.1%.
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38 Table 4 shows the prevalence and RRs for autoimmune diseases in individuals with
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40 first-degree relatives with MI compared with the general population. The RR (95% CI) in
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43 individuals with first-degree relatives with MI was 1.41 (1.00–2.00) for
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46 polymyositis/dermatomyositis, 1.14 (1.01–1.28) for systemic lupus erythematosus, 1.05
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49 (0.76–1.44) for inflammatory bowel disease, 0.98 (0.78–1.23) for myasthenia gravis, 0.95
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52 (0.67–1.35) for vasculitis, 0.94 (0.59–1.48) for systemic sclerosis, 0.84 (0.76–0.92) for
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55 rheumatoid arthritis, and 0.55 (0.32–0.92) for Behçet disease.
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DISCUSSION

In this study, we evaluated the familial aggregation of MI and co-aggregation of autoimmune disease and MI in a population of more than 24 million. This analysis yielded five main findings: First, patients with at least one affected first-degree relative were 1.76-fold more likely to suffer from MI than the general population. The sibling, offspring, parental, paternal and maternal history of MI conferred RRs of MI of 2.35, 2.21, 1.60, 1.72, and 1.53, respectively. Second, for individuals with first-degree relatives with MI, MI events occurred ten years earlier than for the general population, and younger individuals were associated with a higher RR of MI. Third, the more frequently MI occurred in an individual's first-degree relatives, the higher that individual's risk of MI. Fourth, shared environmental and genetic variance played only a minor role in MI susceptibility, but non-shared environmental factors accounted for more than three-quarters of the phenotypic variance in MI. Finally, a family history of MI in first-degree relatives was not associated with an increased risk for a majority of most of autoimmune diseases.

The increased MI risk associated with family history found in our study aligns with results of previous case-controlled and population-based studies.^{3 5 7 9 10 12} A meta-analysis of 12 case-control studies yielded an RR of 1.60 (95% CI 1.44–1.77) for CHD in individuals with an affected relative,⁵ which is similar to our estimate of 1.76 (95% CI 1.68–1.85) for subjects

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4 with affected first-degree relatives. The RRs estimated in some studies were greater than
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6 ours, however.^{7 12} For instance, a nationwide population study in Denmark found high MI
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8 risks in subjects with an affected sibling (RR 4.3, 95% CI 3.53–5.23) or mother (RR 2.4, 95% CI
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10 2.20–2.60),¹² which is higher than our findings for these relationships (RR 2.35, 95% CI 1.96–
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12 2.83 and RR 1.59, 95% CI 1.48–1.70, respectively). The Danish study only included persons
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14 younger than 58 years of age, which is a younger study population than the present study.
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16 Another case-control study, of women aged 18–44 years, also found a higher MI risk in
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18 subjects with affected siblings.²⁶ In the present study, we found that a family history of MI in
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20 first-degree relatives was associated with a higher RR of MI in younger subjects (figure 2).
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22 The more frequently MI occurred in an individual's first-degree relatives, the higher that
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24 individual's risk of MI. Similar findings were also observed in another Danish population
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26 study, which found that a history of MI in second-degree relatives was also associated with
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28 an increased risk of MI.⁹

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40 Although familial aggregation of MI has been shown repeatedly in previous studies,^{17 12} it
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42 still has not been determined whether such aggregation is largely related to shared genes or
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44 environmental factors. Assuming spouses share similar familial environments but not
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46 genetics with other family members, they can be used to estimate the relative contribution
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48 of shared environmental factors to MI susceptibility.²¹⁻²⁴ We found that shared
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50 environmental factors contributed minimally, only around 20% of phenotypic variance of MI
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4 was related to genetics. Non-shared environmental factors accounted for more than
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6 three-quarters of the phenotypic variance of MI. Compared to 43.9% of the genetic
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8 contribution of phenotypic variance in systemic lupus erythematosus,¹⁹ genetic variance in
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10 MI heritability can be regarded as a minor component.¹⁹ Given that multiple risk factors of
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12 MI such as hyperlipidemia, hypertension, and diabetes mellitus have substantial
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14 heritability,²⁷⁻²⁹ the genetic contribution of MI may be even lower.

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20 It is still debatable whether autoimmunity plays an essential role in the development of
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22 atherosclerosis,¹⁴ which is the underlying cause of MI in most cases.³⁰ Patients with
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24 autoimmune diseases are at an increased risk of suffering accelerated atherosclerosis and
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26 premature MI.^{31,32} Despite findings in previous studies suggesting that autoimmune diseases
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28 share part of the pathogenesis of atherosclerosis,^{13, 33} the extent and contributions to
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30 disease manifestation may differ. Atherosclerosis starts with endothelial injury followed by
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32 subendothelial accumulation of low-density lipoproteins, which triggers macrophages and
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34 type one T helper cells to form atherosclerotic plaques.^{34,35} Inflammation is initiated by the
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36 innate immune system oxidizing low-density lipoproteins and is perpetuated by type one T
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38 helper cells that react to autoantigens from the apolipoprotein B100 in low-density
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40 lipoproteins.³⁵ Chronic inflammation activated by the innate immune system is responsible
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42 for most atherosclerosis development, in which autoimmunity only plays a minor role. In the
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44 present study, we found that there was no co-aggregation of autoimmune disease in families
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4 affected by MI. Future studies are needed to confirm our findings.
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6 Our results have several implications. First, the study provides quantitative estimates of
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8 absolute risks and RRs, familial transmission, and the proportion of sporadic cases of MI.
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10 These estimates are valuable in clinical counseling. Compared to the general population,
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12 younger subjects with first-degree relatives with MI were at a higher risk of developing MI in
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14 the future. The absence of co-aggregation between MI and autoimmune diseases suggests
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16 that further evaluation of different pathogenic mechanisms is required.
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23 The size of the cohort and the number of MI cases allowed detailed family history
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25 analyses and contribute to the strength of this study. Additionally, instead of using
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27 self-reported family histories of MI, we used database-linked family histories, which are
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29 more reliable and have been validated. Moreover, self-reported measures of family history
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31 in previous studies often included multiple events (CHD, stroke, death) or cases with varying
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33 severity (stable angina, unstable angina, MI).^{6 36} By comparison, we used only the primary
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35 discharge diagnosis of MI, which is a strict and validated endpoint that is subject to less
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37 misclassification and yields more interpretable estimates.
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49 **Limitations**

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51 Some limitations of the present study should be acknowledged. First, this study was
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53 confined to Taiwan. Although it covered the entire population of Taiwan, the results may not
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4 be generalized and applied to other settings. Second, the NHIRD is primarily a health
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6 insurance database that contains only limited information on clinical diagnosis criteria. We
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9 did not have access to all information concerning traditional MI risk factors, including
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12 smoking, obesity, index, blood pressure, lipid levels, and physical activity. Third, the analysis
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15 of relative genetic and environmental contributions should be interpreted with caution
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18 because it is based on the multifactorial liability model, where the results are subject to
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21 assumptions. However, published data on other diseases, such as schizophrenia and
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24 systemic lupus erythematosus support the validity of this model.^{19 37} Finally, we cannot
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27 account for the effects of assortative mating, whereby spouses are more phenotypically
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30 similar than if mating were to occur at random in a population.
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34 **CONCLUSION**

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37 In this population-based cohort study, MI was found to aggregate in families, and
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40 non-shared environmental factors seemed to contribute more to the phenotypic variance of
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43 MI than genetic factors. There was no co-aggregation of autoimmune disease in families
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46 affected by MI.
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53
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4 and interpreting the data. Part of data was obtained via Applied Health Research Data
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6 Integration Service from the National Health Insurance Administration.
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9 **Contributors** Concept of study: C-F K and S-H C. Study design: C-L W, C-F K, Y-H Y, M-Y H,
10
11 and S-H C. Statistical analysis: C-L W and M-Y H. Interpretation of results: C-L W, M-Y H, C-T
12
13 K, and S-H C. Manuscript writing: C-L W and S-H C. The other authors provided inputs,
14
15 expertise, and critical review of the manuscript.
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19
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21
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26 **Disclaimer** The interpretation and conclusions contained herein do not represent those of
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28 National Health Insurance Administration, Department of Health or National Health
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30 Research Institutes.
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34 **Competing interests** None declared.
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38 **Patient consent** Not required.
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41 **Ethics approval** This study was approved by the Institutional Review Board of Chang Gung
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43 Memorial Hospital and by the National Health Research Institutes, which compile data for
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45 the National Health Insurance Research Database.
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49 **Data sharing statement** Extra data are available by emailing the corresponding author
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51 (afen.chang@gmail.com).
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Table 1 Baseline characteristics of individuals with affected first-degree relatives with myocardial infarction and the general population

	Women			Men		
	≥1 affected Relatives	General population	P value	≥1 affected Relatives	General population	P value
No. of subjects	109371	12272301		149989	12089044	
Age (y), mean (SD)	40.3 (21.0)	39.6 (16.8)	<0.0001	38.9 (20.9)	41.7 (15.6)	<0.0001
MI (%)	376 (0.3)	33 762 (0.3)	<0.0001	1 879 (1.3)	101 507 (0.8)	<0.0001
Place of residence (%)			<0.0001			<0.0001
Urban	76254 (69.7)	7740136 (63.1)		99079 (66.1)	7309940 (60.5)	
Suburban	28195 (25.8)	3624603 (29.5)		43568 (29.1)	3848868 (31.8)	
Rural	4733 (4.3)	872384 (7.11)		7086 (4.7)	895750 (7.4)	

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Unknown	189 (0.2)	35178 (0.3)	256 (0.17)	34486 (0.3)
Income levels (%)			<0.0001	<0.0001
Quintile 1	18783(17.2)	2062900(16.8)	29225 (19.5)	2310684 (19.1)
Quintile 2	15135 (13.8)	1838185(15.0)	15425(10.3)	1506475 (12.5)
Quintile 3	27496 (25.1)	3658895 (29.8)	34394 (22.9)	3207226 (26.5)
Quintile 4	24975 (22.8)	2411506 (19.7)	30457 (20.3)	2241214 (18.5)
Quintile 5	22962 (21.0)	2298595 (18.7)	40466 (27.0)	2821626 (23.3)
Unknown	20 (0.0)	2220 (0.0)	22 (0.0)	1819 (0.0)
Occupation (%)			<0.0001	<0.0001
Dependents of the insured individuals	26186 (23.9)	4535168(37.0)	26276 (17.5)	3746793 (31.0)

Civil servants, teachers, military

personnel and veterans 5481 (5.0) 343851 (2.8) 9 641(6.3) 570 840 (4.7)

Non-manual workers and

professionals 44 824 (41.0) 3642834 (29.7) 61 947 (41.3) 3934252 (32.5)

Manual workers 20894 (19.1) 2609974 (21.3) 30635 (20.4) 2286403 (18.9)

Other 11986 (11.0) 1140474 (9.3) 21490 (14.3) 1550756 (12.8)

Table 2 Relative risks for myocardial infarction in patients with myocardial infarction in first-degree relatives

Type of affected relative	Sex of affected relative	Sex of individual	No. of cases	Absolute risk (%)	Relative risk* (95% CI)
Any	Male	Male	1 198	1.08	1.84 (1.72–1.96)
		Female	307	0.35	1.76 (1.58–1.97)
		All	1 505	0.76	1.92 (1.81–2.03)
	Female	Male	739	1.84	1.52 (1.41–1.63)
		Female	73	0.32	1.69 (1.27–2.25)
		All	812	1.30	1.59 (1.48–1.70)
	All	Male	1 879	1.25	1.67 (1.59–1.76)
		Female	376	0.34	1.74 (1.57–1.93)
		All	2 255	0.87	1.76 (1.68–1.85)
Parent	Male	Male	756	0.74	1.67 (1.55–1.79)
		Female	40	0.05	1.21 (0.89–1.64)
		All	796	0.45	1.72 (1.60–1.84)
	Female	Male	706	1.80	1.50 (1.39–1.61)
		Female	43	0.20	1.25 (0.93–1.69)
		All	749	1.23	1.53 (1.43–1.65)

	All	Male	1 421	1.01	1.56 (1.48–1.64)
		Female	81	0.08	1.22 (0.98–1.51)
		All	1 502	0.63	1.60 (1.52–1.68)
Offspring	Male	Male	302	8.02	2.15 (1.93–2.40)
		Female	260	3.34	1.95 (1.73–2.19)
		All	562	4.87	2.18 (2.01–2.36)
	Female	Male	26	7.60	2.40 (1.66–3.45)
		Female	28	4.75	3.31 (2.32–4.72)
		All	54	5.79	2.94 (2.27–3.80)
	All	Male	326	7.94	2.16 (1.95–2.40)
		Female	286	3.42	2.01 (1.80–2.25)
		All	612	4.91	2.21 (2.05–2.39)
Sibling	Male	Male	154	2.95	2.48 (2.04–3.01)
		Female	9	0.23	1.20 (0.62–2.30)
		All	163	1.77	2.40 (1.99–2.90)
	Female	Male	8	1.49	1.48 (0.74–.98)
		Female	1	0.60	5.24 (0.77–35.54)
		All	10	1.15	1.75 (0.88–3.46)
	All	Male	162	2.81	2.40 (1.99–2.89)

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Female	11	0.25	1.40 (0.74–2.65)
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All	173	1.72	2.35 (1.96–2.83)
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*Adjusted for age, gender, place of residence, quintiles of income levels, occupation and family size. CI, confidence interval.

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Table 3 Age-specific prevalence of myocardial infarction in individuals with a first-degree relative with MI and the general population in Taiwan in 2015

Age, y	First-degree relative with MI			General population		
	Case	Population	Absolute risk, %	Case	Population	Absolute risk, %
0-4	0	1198	0.00	4	1051252	0.00
5-9	0	2671	0.00	4	974384	0.00
10-14	0	5835	0.00	13	1153257	0.00
15-19	0	11300	0.00	37	1505997	0.00
20-24	1	17328	0.01	75	1748236	0.00
25-29	7	23469	0.03	179	1784709	0.01
30-34	40	37278	0.11	595	2095030	0.03
35-39	88	37707	0.23	1788	2157768	0.08
40-44	105	22745	0.46	3539	1853362	0.19
45-49	198	22939	0.86	6550	1865602	0.35
50-54	292	23093	1.26	10845	1877518	0.58
55-59	320	19940	1.60	14980	1737170	0.86
60-64	357	14554	2.48	18926	1521260	1.24
65-69	235	7453	3.15	17146	982469	1.75

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70-74	166	4041	4.11	15303	685355	2.23
75-79	161	3214	5.01	15542	578084	2.69
80-84	139	2235	6.22	13827	407735	3.39
85-89	97	1507	6.44	10510	258837	4.06
≥90	49	847	5.79	5406	123320	4.38

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Table 4 Relative risks (RRs) of autoimmune diseases in subjects with myocardial infarction in first-degree relatives

Autoimmune diseases	Sex	Subjects with MI in first-degree relatives		General population		RR (95% CI)*
		No.	Prevalence, %	No.	Prevalence, %	
Congenital hypothyroidism	Male	27	0.02	4347	0.04	0.95 (0.65–1.38)
	Female	54	0.05	6575	0.05	0.90 (0.69–1.18)
	All	81	0.03	10922	0.04	0.89 (0.71–1.10)
Rheumatoid arthritis	Male	114	0.08	11163	0.09	0.83 (0.69–1.00)
	Female	284	0.26	44686	0.36	0.85 (0.76–0.96)
	All	398	0.15	55849	0.23	0.84 (0.76–0.92)
Sjögren's syndrome	Male	32	0.02	2359	0.02	1.01 (0.70–1.46)
	Female	242	0.22	19315	0.16	1.08 (0.94–1.26)

	All	274	0.11	21674	0.09	1.06 (0.93–1.21)
Systemic lupus erythematosus	Male	28	0.02	2209	0.02	0.91 (0.64–1.29)
	Female	178	0.16	20552	0.17	1.18 (1.04–1.34)
	All	206	0.08	22761	0.09	1.14 (1.01–1.28)
Systemic sclerosis	Male	7	0.00	461	0.00	1.06 (0.51–2.22)
	Female	11	0.01	1615	0.01	0.88 (0.49–1.57)
	All	18	0.01	2076	0.01	0.94 (0.59–1.48)
Polymyositis /Dermatomyositis	Male	9	0.01	646	0.01	0.98 (0.51–1.87)
	Female	22	0.02	1472	0.01	1.74 (1.15–2.62)
	All	31	0.01	2118	0.01	1.41 (1.00–2.00)
Behçet disease	Male	7	0.00	883	0.01	0.53 (0.25–1.12)
	Female	7	0.01	1186	0.01	0.58 (0.28–1.21)

	All	14	0.01	2069	0.01	0.55 (0.32–0.92)
Vasculitis	Male	23	0.02	3087	0.03	1.07 (0.71–1.60)
	Female	10	0.01	1958	0.02	0.79 (0.43–1.47)
	All	33	0.01	5045	0.02	0.95 (0.67–1.35)
Inflammatory Bowel Disease	Male	32	0.02	1798	0.01	1.21 (0.86–1.70)
	Female	5	0.00	1009	0.01	0.56 (0.23–1.34)
	All	37	0.01	2807	0.01	1.05 (0.76–1.44)
Multiple Sclerosis	Male	0	0.00	354	0.00	0.18 (0.03–1.27)
	Female	12	0.01	1234	0.01	0.97 (0.56–1.71)
	All	13	0.01	1588	0.01	0.73 (0.42–1.25)
Myasthenia gravis	Male	41	0.03	2820	0.02	1.11 (0.82–1.50)
	Female	34	0.03	4312	0.04	0.87 (0.62–1.21)

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	All	75	0.03	7132	0.03	0.98 (0.78–1.23)
Type 1 diabetes mellitus	Male	86	0.06	4884	0.04	0.96 (0.78–1.18)
	Female	91	0.08	5841	0.05	0.99 (0.82–1.21)
	All	177	0.07	10725	0.04	0.98 (0.85–1.13)

*Adjusted for age, gender, place of residence, quintiles of income levels, occupation, family size and Charlson comorbidity index.

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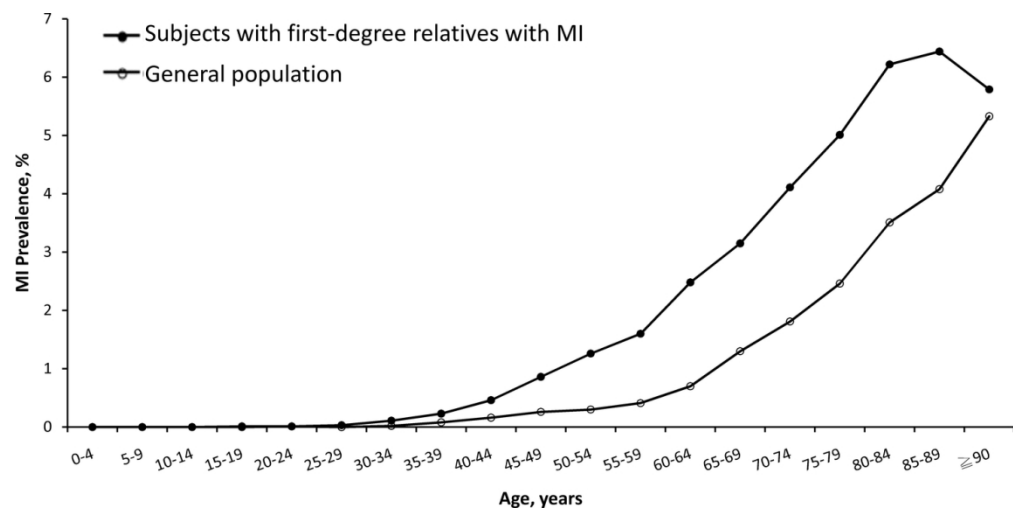
Figure Legends

Figure 1. Age-specific prevalence of myocardial infarction (MI) in subjects with MI in first-degree relatives and in the general population in Taiwan in 2015.

Figure 2. The relative risk of MI in subjects with affected first-degree relatives stratified by the age of the evaluated subjects compared to the general population.

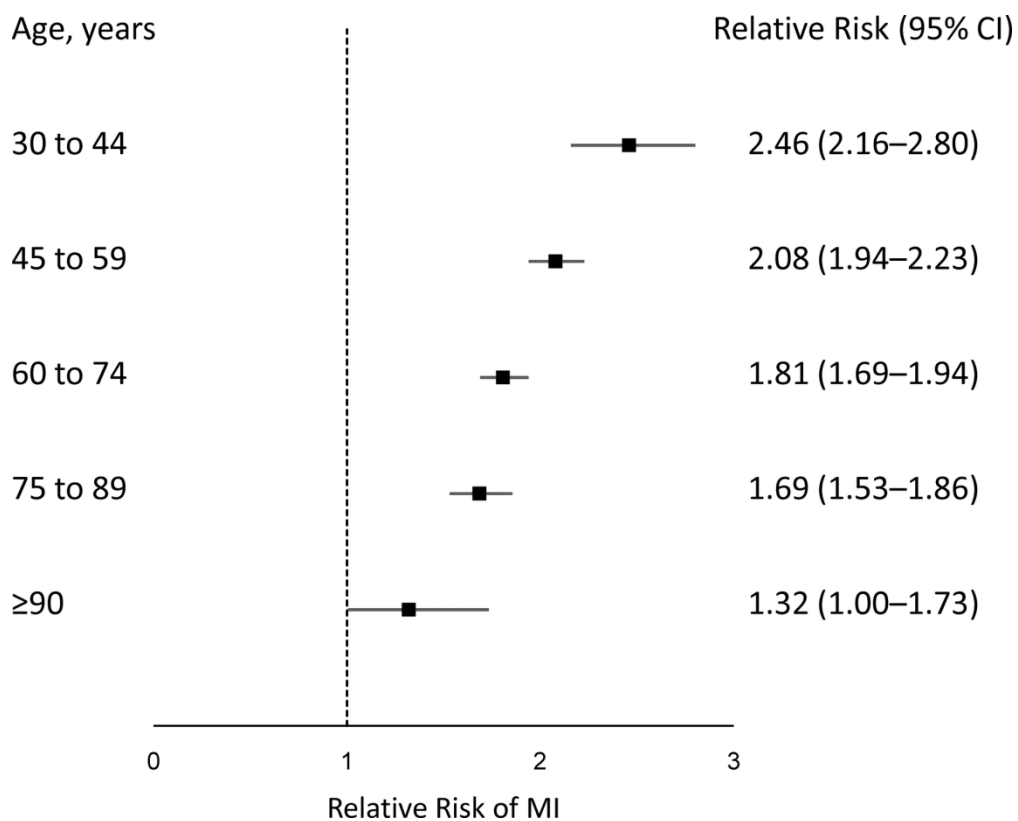
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Age-specific prevalence of myocardial infarction (MI) in subjects with MI in first-degree relatives and in the general population in Taiwan in 2015.

124x61mm (300 x 300 DPI)



The relative risk of MI in subjects with affected first-degree relatives stratified by the age of the evaluated subjects compared to the general population.

162x130mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Page 5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 5-6
Bias	9	Describe any efforts to address potential sources of bias	Page 7
Study size	10	Explain how the study size was arrived at	Pages 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Pages 7-8
		(b) Describe any methods used to examine subgroups and interactions	Pages 7-8
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	Pages 7-8

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9
		(b) Give reasons for non-participation at each stage	Page 9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 9
		(b) Indicate number of participants with missing data for each variable of interest	Page 9
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Pages 9-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.