Introduction

Myocardial infarction (MI) is a leading cause of death worldwide, and is a multifactorial disease, influenced by genetic and environmental factors [1]. The main risk factors for MI include hypertension, hypercholesterolemia, diabetes, obesity, and smoking. In addition, recent studies have also shown the importance of genetic factors caused by polymorphisms in the pathogenesis of MI [2–7]. Apolipoprotein E (Apo E) is a serum glycoprotein found in circulating chylomicrons (remnants), very low density lipoproteins, intermediate density lipoproteins and high-density lipoproteins [8]. ApoE is considered as an excellent candidate gene for studying the susceptibility to coronary heart disease (CHD) and MI because of its pivotal roles in the metabolism of cholesterol and triglyceride [9]. The most extensively studied polymorphism in the ApoE gene codes for three variant alleles: e2, e3 and e4, which yield six possible genotypes: e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 and e4/e4 in general population [10]. The products of the three alleles differ in their properties such as affinity for binding low density lipoprotein receptors and lipoprotein particles; therefore, this ApoE polymorphism could affect the serum levels of cholesterol and triglyceride, thus contributing to the progression of atherosclerosis. In fact, ApoE polymorphisms have been found to be associated with many lipid-related diseases and cardiovascular and cerebrovascular diseases [11–14].

Numerous studies have been conducted to explore the association of this ApoE polymorphism and CHD; some of the studies found a significant association between the ApoE e4 allele and CHD [15–17]. A meta-analysis conducted in 2004 provided evidence that the e4 allele of ApoE was a risk factor for the development of CHD [18]. Another meta-analysis conducted in 2013 further confirmed this finding in a Chinese population [19]. However, no meta-analysis has been conducted to explore the association between this ApoE gene polymorphism and MI. In spite of the presence of advanced CHD, only a subset of patients develops MI during their life. The reasons for these individual differences in susceptibility to MI are poorly understood. Therefore, it is important to explore the association between ApoE gene polymorphisms and MI. In fact, a number of case-control studies have been conducted to clarify the association between ApoE gene polymorphisms and MI [20–52]; however, the results are inconsistent. Therefore, we conducted this meta-analysis including all of the evidence produced to date to explore this issue.

Materials and Methods

Search strategy

We searched all published studies in the Pubmed database (up to January 20, 2014) using the following combination of keywords: “Apolipoprotein E” OR “ApoE” AND “acute coronary syndrome” OR “myocardial infarction” AND “polymorphism” OR

Abstract

A number of case-control studies have been conducted to clarify the association between ApoE polymorphisms and myocardial infarction (MI); however, the results are inconsistent. This meta-analysis was performed to clarify this issue using all the available evidence. Searching in PubMed retrieved all eligible articles. A total of 33 studies were included in this meta-analysis, including 18752 MI cases and 18963 controls. The pooled analysis based on all included studies showed that the MI patients had a decreased frequency of the e2 allele (OR = 0.78, 95% CI = 0.70–0.87) and an increased frequency of the e4 allele (OR = 1.15, 95% CI = 1.10–1.20); The results also showed a decreased susceptibility of MI in the e2/e3 vs. e3/e3 analysis (OR = 0.79, 95% CI = 0.68–0.90) and in the e2 vs. e3 analysis (OR = 0.78, 95% CI = 0.69–0.89), an increased susceptibility of MI in the e3/e4 vs. e3/e3 analysis (OR = 1.26, 95% CI = 1.12–1.41), in the e4 vs. e3 analysis (OR = 1.22, 95% CI = 1.12–1.32) and in the e4/e4 vs. e3/e3 analysis (OR = 1.59, 95% CI = 1.15–2.19). However, there were no significant associations among polymorphisms and MI for the following genetic models: frequency of the e3 allele (OR = 0.99, 95% CI = 0.96–1.02); e2/e3 vs. e3/e3 analysis (OR = 0.73, 95% CI = 0.40–1.32); or e2/e4 vs. e3/e3 analysis (OR = 1.10, 95% CI = 0.99–1.21). Our results suggested that the e4 allele of ApoE is a risk factor for the development of MI and the e2 allele of ApoE is a protective factor in the development of MI.
“polymorphisms” OR “variants” OR “variant”. In addition, manual searches for related articles were also performed to avoid missing any relevant studies.

**Inclusion and exclusion criteria**

The inclusion criteria for identified articles were as follows: 1) Case-control studies with full text articles on the relationship of ApoE polymorphisms and MI; 2) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). Those not designed as case-control studies, systemic reviews, those not written in English or Chinese, and those that provided no usable data, were excluded.

**Data extraction**

Two authors independently extracted the data from all included studies using a predesigned data extraction table. The following information was extracted from each included article: first author, year of publication, ethnicity and country, source of controls, total numbers of MI cases and controls, distribution of genotypes and alleles in MI cases and controls, and evidence of conforming to the Hardy-Weinberg equilibrium (HWE).

**Statistical analysis**

We firstly used chi-squared ($\chi^2$) test and $I^2$ statistic to assess heterogeneity across studies. A fixed effect model (Mantel–Haenszel) was used in the absence of heterogeneity. Otherwise, the random effect model (DerSimonian–Laird) was adopted. The strength of the association between the ApoE gene polymorphism and MI was assessed by odds ratios (ORs) with the corresponding 95% CI for each study. The ORs and their 95% CIs were assessed for the following seven genetic models: 1) $e_2e_2$ vs. $e_3e_3$; 2) $e_2e_3$ vs. $e_3e_3$; 3) $e_2e_4$ vs. $e_3e_3$; 4) $e_3e_4$ vs. $e_3e_3$; 5) $e_4e_4$ vs. $e_3e_3$; 6) $e_2$ vs. $e_3$; 7) $e_4$ vs. $e_3$. The allele frequencies of $e_2$, $e_3$ and $e_4$ were also assessed using the same method. Cumulative meta-analysis was also performed for the above genetic models. Subgroup analysis for ethnicity (Asian and Caucasian) was also performed. To find potential outliers, influence analysis was performed by omitting each study in turn. A funnel plot, calculated using Begg’s and Egger’s tests, was adopted for assessing potential publication bias. Statistical analysis was conducted using STATA statistical software (version 11; StataCorp, College Station, Texas, USA). A P value less than 0.05 was considered statistically significant.

**Results**

**Literature selection and study characteristics**

One hundred and thirty two articles were retrieved from PubMed, 79 of which were excluded after screening the titles and abstracts (58 were irrelevant studies, 13 were reviews and eight were not published in English or Chinese). Fifty-three articles were selected for detailed assessment, which excluded a further 20 articles (seven were not case-control studies, eight had no usable data (no case and control numbers according to the genotypes) and five were not about MI). Finally, 33 studies were included in this meta-analysis, which included 18752 MI cases and 18963 controls. The detailed selection procedure is shown in Figure 1. There were three studies did not follow the HWE. The detailed characteristics of the included studies are shown in Table 1. The present study met the PRISMA statement requirements (Checklist S1 and Figure 1).

![Flowchart of the study selection](https://doi.org/10.1371/journal.pone.0104608.g001)
## Table 1. Detailed characteristics of studies included in this meta-analysis.

| Study [Reference] | Year | Country | Ethnicity | Study type | HWE | Total sample size | Genotypes distribution (Cases/controls) |
|-------------------|------|---------|-----------|------------|-----|-------------------|-----------------------------------------|
| Utermann 1984[20]  | 1984 | Germany | Caucasian | HCC | Yes | 523/1031 | 7/120 x6/124 333/617 11/15 92/236 12/29 86/359 493/977 115/280 |
| Cuming 1984[21]    | 1984 | Scotland | Caucasian | PCC | Yes | 239/400 | 0/2 18/51 128/233 10/11 77/99 6/4 28/64 223/383 93/114 |
| Lenzen 1986[22]    | 1986 | France   | Caucasian | PCC | Yes | 570/624 | 1/6 50/67 360/393 10/20 137/125 12/13 61/93 547/585 159/158 |
| Eichner 1993[23]   | 1993 | USA      | Caucasian | PCC | Yes | 114/412 | 0/2 16/35 67/276 0/4 30/85 1/10 16/41 113/396 31/99 |
| Luc 1994[24]       | 1994 | France   | Caucasian | PCC | Yes | 574/680 | 3/6 54/92 352/428 14/14 133/126 18/14 71/112 539/666 165/154 |
| HERGENC 1995[25]   | 1995 | Turkey   | Caucasian | HCC | Yes | 50/60  | 0/0 7/6 41/47 0/2 2/5 0/0 7/8 50/58 2/7 |
| Kim 1995[26]       | 1995 | Korea    | Asian     | HCC | Yes | 97/137 | 2/1 17/25 57/95 0/4 20/12 1/0 19/30 94/132 21/16 |
| Nakai 1998[27]     | 1998 | Japan    | Asian     | PCC | Yes | 254/422 | 0/0 10/16 178/327 2/4 52/74 6/1 12/20 240/417 60/79 |
| Scaglione 1999[28] | 1999 | Italy    | Caucasian | PCC | No  | 98/98  | NR  NR  NR  NR  3/3  NR  84/87 11/8 |
| Lamert 2000[29]    | 2000 | France   | Caucasian | PCC | Yes | 567/678 | 3/4 67/100 332/430 0/3 152/138 18/13 70/107 551/658 170/154 |
| Benes 2000[30]     | 2000 | Czech    | Caucasian | PCC | Yes | 114/222 | 1/0 12/30 71/147 3/2 23/43 4/0 16/32 106/220 30/45 |
| Batalla 2000[31]   | 2000 | Spain    | Caucasian | PCC | Yes | 220/200 | 0/0 9/18 174/151 1/1 32/28 4/2 10/19 215/197 37/31 |
| Ralová 2001[32]    | 2001 | Canada   | Caucasian | PCC | Yes | 69/69  | 2/1 8/5 46/47 1/0 11/15 1/1 11/6 65/67 13/16 |
| Bai 2001[33]       | 2001 | China    | Asian     | PCC | Yes | 47/50  | 0/0 4/5 40/39 0/0 6/3 0/0 4/5 50/47 6/3 |
| Freitas 2002[34]   | 2002 | Australia| Caucasian | PCC | Yes | 411/624 | 3/4 24/67 254/372 9/15 11/147 10/19 36/86 389/586 130/181 |
| Mamotte 2002[35]   | 2002 | Australia| Caucasian | PCC | Yes | 359/659 | 4/4 24/68 217/383 7/16 96/149 11/19 35/88 337/600 114/184 |
| Kolovou 2002[36]   | 2002 | Greece   | Caucasian | PCC | Yes | 124/240 | 0/0 3/34 94/159 0/5 27/40 0/2 3/39 124/233 27/47 |
| Keaveny 2003[37]   | 2003 | UK       | Caucasian | PCC | Yes | 448/757 | NR  440/686 2566/3384 NR 1206/1376 NR 440/686 421/5446 1206/1376 |
| Kolovou 2003[38]   | 2003 | Greece   | Caucasian | PCC | Yes | 165/165 | 0/0 3/16 129/118 1/4 29/23 1/0 4/20 161/157 31/27 |
| Kumar 2003[39]     | 2003 | India    | Caucasian | PCC | Yes | 35/45  | 0/2 6/9 12/32 1/0 6/0 10/2 7/9 24/41 17/2 |
| Marques 2003[40]   | 2003 | France   | Caucasian | HCC | Yes | 400/338 | NR  NR 272/228 NR  NR  NR 37/40 272/228 91/70 |
| Keaveny 2004[41]   | 2004 | UK       | Caucasian | PCC | Yes | 4685/3460 | NR  440/406 2566/1949 1206/810 NR 1646/1216 3006/2355 1206/810 |
| Ranjith 2004[42]   | 2004 | South Africa | Caucasian | PCC | Yes | 195/300 | 0/3 7/18 139/228 3/3 45/43 1/5 10/24 191/289 49/51 |
| Baum 2006[43]      | 2006 | China    | Asian     | PCC | Yes | 231/331 | 0/2 13/60 164/203 4/6 46/39 4/1 17/68 223/302 54/46 |
| Aasvee 2006[44]    | 2006 | Estonia  | Caucasian | PCC | Yes | 71/85  | 1/1 4/13 45/52 2/3 16/16 3/0 7/17 65/81 21/19 |
| Koch 2008[45]      | 2008 | Germany  | Caucasian | PCC | Yes | 3657/1211 | 26/7 402/164 2729/736 63/23 809/263 78/18 491/194 3490/1163 950/304 |
| Kolovou 2009[46]   | 2009 | Greece   | Caucasian | PCC | Yes | 124/240 | NR  NR  NR  NR  NR  NR 5/19 106/197 13/24 |
| Bahri 2008[47]      | 2008 | Tunisia  | Caucasian | PCC | Yes | 80/100 | 0/0 6/8 61/78 0/1 13/13 0/0 6/9 80/199 13/14 |
| Martinelli 2009[48] | 2009 | Italy    | Caucasian | HCC | Yes | 394/287 | NR  NR  NR  NR  NR  NR 34/25 285/220 76/42 |
| Al-Bustan 2009[49]  | 2009 | Kuwait   | Caucasian | HCC | No  | 88/122 | 4/9 2/2 72/98 2/3 8/9 0/1 6/11 90/33 16/5 |
| Onrat 2012[50]     | 2012 | Turkey   | Caucasian | PCC | Yes | 36/100 | 0/0 12/4 72/27 0/0 16/4 0/1 12/4 100/35 16/5 |
| Tanguturi 2013[51]  | 2013 | USA      | Caucasian | HCC | Yes | 202/210 | 0/0 8/14 121/167 4/3 37/23 11/3 12/17 187/204 52/29 |
Quantitative data synthesis

The meta-analysis of the included studies showed that there was significant association between the ApoE gene polymorphism and MI. The results showed that the MI patients had a decreased frequency of the e2 allele (OR = 0.78, 95% CI = 0.70–0.87, Figure 2) and an increased frequency of the e4 allele (OR = 1.15, 95% CI = 1.10–1.20, Figure 3). The results also showed a decreased susceptibility of MI in the e2/e3 vs. e3/e3 analysis (OR = 0.79, 95% CI = 0.69–0.89, Figure S4), and in the e2 vs. e3 analysis (OR = 0.78, 95% CI = 0.69–0.89, Figure S4), and an increased susceptibility of MI in the e3/e4 vs. e2/e3 analysis (OR = 1.26, 95% CI = 1.12–1.41, Figure S2) in the e2/e4 vs. e3/e3 analysis (OR = 1.59, 95% CI = 1.15–2.19, Figure S3) and in the e4 vs. e3 analysis (OR = 1.22, 95% CI = 1.12–1.32, Figure S5).

However, there were no significant associations among polymorphisms and MI for the following genetic models: frequency of e3 allele (OR = 0.99, 95% CI = 0.96–1.02); e2/e2 vs. e3/e3 analysis (OR = 0.73, 95% CI = 0.40–1.32); e2/e4 vs. e3/e3 analysis (OR = 1.10, 95% CI = 0.99–1.21). The detailed results are shown in Table 2. Cumulative analysis further confirmed the results (Figure 4 and Figure S6).

Tests of heterogeneity and subgroup analysis

Significant between-study heterogeneity existed in the analyses of seven genetic models: e2/e2 vs. e3/e3 (p = 0.005); e2/e3 vs. e3/e3 (p = 0.001); e3/e4 vs. e3/e3 (p = 0.001); e4/e4 vs. e3/e3 (p = 0.04), e2 vs. e3 (p = 0.04), e2 vs. e3 (p = 0.02) and the e2 allele frequency (p = 0.001). A random effects model was adopted for these analyses.

Furthermore, we performed subgroup analysis based on ethnicity and found a decreased susceptibility of MI in the e2/e3 vs. e3/e3 analysis (OR = 0.80, 95% CI = 0.70–0.92) and e2 allele frequency (OR = 0.79, 95% CI = 0.71–0.88) among Caucasian populations. We also found an increased susceptibility of MI in the e3/e4 vs. e3/e3 analysis (OR = 1.23, 95% CI = 1.09–1.38), e4/e4 vs. e3/e3 analysis (OR = 1.47, 95% CI = 1.07–2.02) and the e4 allele frequency (OR = 1.14, 95% CI = 1.09–1.19) among Caucasian populations. Among Asian populations, we also found an increased susceptibility of MI in the e3/e4 vs. e3/e3 analysis, e4/e4 vs. e3/e3 analysis and for the e4 allele frequency; the detailed results are shown in Table 2.

Sensitivity analysis

We conducted influence analysis to assess the sensitivity of each individual study on the pooled ORs by sequential omission of each individual study. The results suggested that no individual study significantly affected the pooled ORs in the e2 allele and e4 allele frequency analysis (Figure 5), and in the e2/e3 vs. e3/e3 analysis, e3/e4 vs. e3/e3 analysis and e4/e4 vs. e3/e3 analysis (Figure S7).

Publication bias

Funnel plots examined potential publication bias qualitatively and no obvious asymmetry was observed in any genetic model, as shown in Figure 6. Furthermore, the results from Begg’s and Egger’s tests did not provide any evidence of publication bias (Table S1).

Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the association between an ApoE polymorphism and susceptibility of MI. In this meta-analysis, we discovered an increased susceptibility of MI in the e4 allele frequency analysis. Moreover, the individuals with e2/e4 genotype, e3/e4 genotype and
ε4 genotype had a significantly higher susceptibility of developing MI compared to those with the ε3ε3 genotype. Therefore, it is reasonable to assume that the ε4 allele of ApoE is a risk factor for the development of MI. These results were consistent with a previous meta-analysis, which showed that the ε4 allele of ApoE is a risk factor for the development of CHD [11,12]. In addition, we found a decreased susceptibility of MI in the ε2 allele frequency analysis and in the ε2ε3 vs. ε3ε3 analysis, which indicate that the ε2 allele is a protective factor in the development of MI. Cumulative meta-analysis also confirmed these findings. Considering the large sample size in the pooled analysis in this meta-analysis, we believe that our results are robust and reliable.

ApoE is a multifunctional protein that plays an important role in the metabolism of cholesterol and triglycerides, by binding to its receptors to help mediate clearance of chylomicron and remnant particles [53]. The three common isoforms, ε2, ε3 and ε4, have different receptor-binding abilities and could yield different circulating levels of cholesterol and triglycerides. Compared with ε3 homozygotes, carriers of the ε2 allele have lower circulating cholesterol levels, whereas carriers of the ε4 allele appear to have higher plasma levels of total and low-density lipoprotein cholesterol [54]. According to these mechanisms, our meta-analysis suggested that carrying the ε4 allele is a risk factor for MI and that the ε2 allele has a protective role in the development of MI. When stratifying the studies by ethnicity, the ε4 allele remained a risk factor.
factor and the ε2 allele was still protective in the development of MI among Caucasian populations; however, only the ε4 allele remained as a risk factor for MI among Asian population. This may be due to the small sample size in the analysis among Asian populations; in fact, there were only four studies that included Asian populations [19,20,26,36]. Therefore, further studies are warranted among Asian populations. In addition, genotype distributions in the controls from Scaglione’s study [28], Bustan’s study [49] and Zende’s study [52] were not in agreement with HWE, therefore, the results may be biased. However, sensitivity analysis suggested that the pooled results were not significantly changed after excluding the three studies (data not shown). This may be due to the large sample size even though the three studies were excluded.

Although the primary results of this meta-analysis are suggestive, some limitations still exist. First, between-study heterogeneity existed in some of the genetic model analysis, which may have affected the results of the present meta-analysis, although a random effects model was adopted for these analyses. Second, publication bias may have occurred because our analyses were based wholly on published studies only in English and Chinese. Third, the results of this meta-analysis were based on unadjusted
estimates because of the lack of adjusted estimates. Currently, some risk factors have been identified for MI, such as hypertension, hypercholesterolemia, diabetes, obesity and smoking. A more precise analysis should be performed if these data could be extracted from primary articles.

In conclusion, this comprehensive meta-analysis has evaluated all published data currently available on the association between the ApoE polymorphism and MI. Our meta-analysis suggested that the e4 allele of ApoE is an risk factor for the development of MI and the e2 allele of ApoE is a protective factor in the development of MI. This may be explained by the fact that e4

Table 2. Results of meta-analysis of ApoE polymorphism and MI.

| Analysis | Overall | Caucasian | Asian |
|----------|---------|-----------|-------|
|         | OR (95% CI) | P/P_het | OR (95% CI) | P/P_het | OR (95% CI) | P/P_het |
| €2 vs. €3 | 0.73 (0.40–1.32) | 0.29/0.005 | 0.70 (0.38–1.31) | 0.27/0.004 | 1.07 (0.08–13.78) | 0.96/0.18 |
| €2 vs. €3 | 0.79 (0.68–0.90) | 0.001/0.001 | 0.80 (0.70–0.92) | 0.001/0.008 | 0.70 (0.31–1.60) | 0.84/0.007 |
| €2 vs. €3 | 1.10 (0.99–1.21) | 0.07/0.70 | 1.10 (1.00–1.21) | 0.05/0.63 | 0.66 (0.26–1.70) | 0.39/0.61 |
| €2 vs. €3 | 1.26 (1.12–1.41) | <0.001/0.001 | 1.23 (1.09–1.38) | 0.001/0.001 | 1.51 (1.14–2.00) | 0.004/0.39 |
| €2 vs. €3 | 1.59 (1.15–2.19) | 0.005/0.04 | 1.47 (1.07–2.02) | 0.02/0.05 | 6.95 (1.75–27.65) | 0.006/0.85 |
| €2 vs. €3 | 0.78 (0.69–0.89) | <0.001/0.001 | 0.80 (0.71–0.90) | <0.001/0.004 | 0.67 (0.37–1.23) | 0.20/0.02 |
| €2 vs. €3 | 1.22 (1.12–1.32) | <0.001/0.002 | 1.20 (1.10–1.30) | <0.001/0.002 | 1.49 (1.15–1.93) | 0.002/0.001 |
| €2 allele frequency | 0.78 (0.70–0.87) | <0.001/0.001 | 0.79 (0.71–0.88) | <0.001/0.005 | 0.65 (0.38–1.13) | 0.13/0.09 |
| €3 allele frequency | 0.99 (0.96–1.02) | 0.38/1.00 | 0.99 (0.96–1.02) | 0.39/1.00 | 0.99 (0.86–1.13) | 0.22/0.94 |
| €4 allele frequency | 1.15 (1.10–1.20) | 0.001/0.17 | 1.14 (1.09–1.19) | 0.001/0.18 | 1.47 (1.14–1.89) | 0.003/0.70 |

P, p value of the test on the association estimate; Phet, p value of the heterogeneity test.

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Figure 4. Cumulative meta-analysis of ApoE gene polymorphism and MI risk: A) €2 allele frequency analysis; B) €4 allele frequency analysis.

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Figure 5. Influence analysis of ApoE gene polymorphism and MI risk: A) ε2 allele frequency analysis; B) ε4 allele frequency analysis.
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allele of ApoE elevates the plasma levels of total and low-density lipoprotein cholesterol while the e2 allele of ApoE lowers the circulating cholesterol levels. Further studies with larger sample sizes are warranted among Asian populations.

Supporting Information

Figure S1  Forest plot for ApoE gene polymorphism and MI risk in the genetic model of e2 vs. e3 frequency analysis. (TIF)

Figure S2  Forest plot for ApoE gene polymorphism and MI risk in the genetic model of e4 vs. e3 frequency analysis. (TIF)

Figure S3  Forest plot for ApoE gene polymorphism and MI risk in the genetic model of e4 vs. e3 frequency analysis. (TIF)

Figure S4  Forest plot for ApoE gene polymorphism and MI risk in the genetic model of e2 vs. e3 frequency analysis. (TIF)

Figure S5  Forest plot for ApoE gene polymorphism and MI risk in the genetic model of e4 vs. e3 frequency analysis. (TIF)

Figure S6 Cumulative meta-analysis of ApoE gene polymorphism and MI risk: A) e2 vs. e3 analysis; B) e3 vs. e4 analysis; C) e4 vs. e3 analysis. (TIF)

Figure S7 Influence analysis of ApoE gene polymorphism and MI risk: A) e2 vs. e3 analysis; B) e3 vs. e4 analysis; C) e4 vs. e3 analysis. (TIF)

Table S1  Results of Egger’s and Begger’s test. (XLS)

Checklist S1 PRISMA Checklist. (DOC)

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Author Contributions

Conceived and designed the experiments: AC HX QZ. Performed the experiments: HX HL JL DZ ZW AC QZ. Analyzed the data: HX HL JL DZ ZW. Contributed reagents/materials/analysis tools: HX HL JL DZ ZW. Wrote the paper: AC HX QZ.

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