PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Familial Aggregation of Myocardial Infarction and Co-aggregation of Myocardial Infarction and Autoimmune Disease: a Nationwide Population-Based Cross-Sectional study in Taiwan
AUTHORS	Chang, Shang-Hung; Wang, Chun-Li; Kuo, Chang-Fu; Yeh, Yung-Hsin; Hsieh, Mei-Yun; Kuo, Chi-Tai

VERSION 1 - REVIEW

REVIEWER	Christina Lee
	Aalborg University Hospital, Unit of Epidemiology and Biostatistics
REVIEW RETURNED	27-Jun-2018

GENERAL COMMENTS	SUMMARY:
	The study " Familial Aggregation of Myocardial Infarction and Co-aggregation of Myocardial Infarction and Autoimmune Disease: a Nationwide Population-Based Cross-Sectional Study in Taiwan" by Wang et al is a Nationwide population-based cross-sectional study using data from the National Health Insurance Research Database from Taiwan in the period 1996-2015. The authors investigated the relative risk (RR) of myocardial infarction (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. The authors found that individuals with a first-degree relative with a history of MI had a higher risk of MI than the general population. Non-shared environmental factors contributed more significantly to MI susceptibility than did heritability and shared environmental factors. They did not find a family history of MI associated with an increased risk of autoimmune disease.
	COMMENTS:
	Thank you for the opportunity to comment on your study, which investigates several hypotheses in one article.
	- Why was the cross-sectional study choosen as a study design?
	- Could you clarify why there were no adjusted analyses and just stratified according to groups?
	- Regarding "The case definition of MI was a patient with a primary discharge diagnosis of MI as defined in the International Classification of Diseases Ninth Revision code." why were all patient ages included, example should it still be considered a family history of MI if your 90 year old parent gets diagnosed with an MI?

	- Under covariates: "Factors that may confound or modify family associations were considered, including age, sex, family size, Charlson Comorbidity Index, and socioeconomic factors (place of residence, occupation, and income level)." What is meant by considered? - Under Discussion: "Our results support the notion that atherosclerosis should be regarded as a chronic inflammatory disease rather than an autoimmune disease." Could you please clarify this conclusion based on your findings?

REVIEWER	Samantha Seals, PhD, Assistant Professor University of West Florida United States of America
REVIEW RETURNED	02-Sep-2018

GENERAL COMMENTS	Statistics used are appropriate and well-described. Limitation section is very good.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Christina Lee

Institution and Country: Aalborg University Hospital, Unit of Epidemiology and Biostatistics

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

SUMMARY:

The study " Familial Aggregation of Myocardial Infarction and Co-aggregation of Myocardial Infarction and Autoimmune Disease: a Nationwide Population-Based Cross-Sectional Study in Taiwan" by Wang et al is a Nationwide population-based cross-sectional study using data from the National Health Insurance Research Database from Taiwan in the period 1996-2015. The authors investigated the relative risk (RR) of myocardial infarction (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. The authors found that individuals with a first-degree relative with a history of MI had a higher risk of MI than the general population. Non-shared environmental factors contributed more significantly to MI susceptibility than did heritability and shared environmental factors. They did not find a family history of MI associated with an increased risk of autoimmune disease.

COMMENTS:

Thank you for the opportunity to comment on your study, which investigates several hypotheses in one article.

- Why was the cross-sectional study chosen as a study design?

Response: Cross-sectional study designs can be used for population-based surveys to assess the absolute risk and relative risk of diseases in patients with exposure. In this study, we wanted to know the risks of myocardial infarction (MI) and autoimmune disease in individuals who have at least one first-degree relative affected by MI. We calculated the cases of MI in individuals with affected relatives, and compared with the whole population. This study drew from 24361345 individuals who were enrolled 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. 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. We found that individuals with affected first-degree relatives had a higher risk of MI than the general population. We did not find a family history of MI associated with an increased risk of autoimmune disease. This information will be useful for designing future cohort studies.

- Could you clarify why there were no adjusted analyses and just stratified according to groups?

Response: There were adjusted analyses in the present study. Relative risks of myocardial infarction were adjusted for age, gender, place of residence, quintiles of income levels, occupation and family size. We apologize for the confusion caused by the imprecise word used in the Methods section. We have replaced the word "considered" with "adjusted".

Page 8

Covariates

Factors that may confound or modify family associations were adjusted, including age, sex, family size, Charlson Comorbidity Index, and socioeconomic factors (place of residence, occupation, and income level).

Page 26

Table 2, right-handed column

Relative risk* (95% CI)

Page 28

Table 2, footnote

*Adjusted for age, gender, place of residence, quintiles of income levels, occupation and family size. CI, confidence interval.

- Regarding "The case definition of MI was a patient with a primary discharge diagnosis of MI as defined in the International Classification of Diseases Ninth Revision code." why were all patient ages included, example should it still be considered a family history of MI if your 90 year old parent gets diagnosed with an MI?

Response: In this population-based study, we evaluated the familial aggregation of MI and co-aggregation of myocardial infarction and autoimmune disease. We want to know the risks of myocardial infarction (MI) and autoimmune disease in individuals who have at least one first-degree relative affected by MI. We calculated the absolute and relative risks of MI in individuals with affected relatives, and compared the result with that of the whole population. In the present study, we included affected relatives of any age, and we did not evaluate the effect of age of affective relatives on the individual's risk of MI. We agree with the reviewer's comment that a family history of MI in a 90 year-old parent may have a different meaning from that in a 60 year-old parent.

- Under covariates: "Factors that may confound or modify family associations were considered, including age, sex, family size, Charlson Comorbidity Index, and socioeconomic factors (place of residence, occupation, and income level)." What is meant by considered?

Response: We have replaced the word "considered" with "adjusted.

Page 8, Methods

Covariate

Factors that may confound or modify family associations were adjusted, including age, sex. Family size, Charlson Comorbidity index and socioeconomic factors (place of residence, occupation, and income level).

- Under Discussion: "Our results support the notion that atherosclerosis should be regarded as a chronic inflammatory disease rather than an autoimmune disease." Could you please clarify this conclusion based on your findings?

Response: Thank you for the comment. We did not find adequate evidence to support the notion that "atherosclerosis should be regarded as a chronic inflammatory disease rather than an autoimmune disease." We have removed this statement and replaced it with "Future studies are needed to confirm our findings."

Page 14, discussion

In the present study, we found that there was no co-aggregation of autoimmune disease in families affected by MI. Future studies are needed to confirm our findings.

Reviewer: 2

Reviewer Name: Samantha Seals, PhD, Assistant Professor

Institution and Country: University of West Florida, United States of America

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Statistics used are appropriate and well-described. Limitation section is very good.