

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	An Enquiry based on a Standardised Questionnaire into Knowledge, Awareness and Preferences concerning the Care of Familial Hypercholesterolemia among Primary Care Physicians in the Asia-Pacific region: The "Ten Countries Study"
AUTHORS	Pang, Jing; Hu, Miao; Lin, Jie; Miida, Takashi; Nawawi, Hapizah; Park, Jeong Euy; Wu, Xue; Ramli, Anis Safura; Kim, Ngoc Thanh; Kwok, See; Gonzales, Lourdes Ella; Su, Ta-Chen; Truong, Thanh Huong; Soran, H; Yamashita, Shizuya; Tomlinson, Brian; Watts, Gerald

VERSION 1 - REVIEW

REVIEWER	Professor Claudia Stefanutti, MD, PhD Extracorporeal Therapeutic Techniques Unit Lipid Clinic and Atherosclerosis Prevention Centre Immunohematology and Transfusion Medicine 'Umberto I' Hospital Department of Molecular Medicine 'Sapienza' University of Rome Rome, ITALY
REVIEW RETURNED	29-May-2017

GENERAL COMMENTS	<p>The study was aimed at assessing physicians' knowledge, awareness and preferences regarding the care of familial hypercholesterolaemia (FH) in the Asia-Pacific region, and carried out utilising a questionnaire to be anonymously completed by physicians from different countries/regions in the Asia-Pacific.</p> <p>The study is original and interesting. However, it would be of interest and desirable for the Reader to provide a copy of the questionnaire to be reported as supplemental file, as the questionnaire is the principal method utilised by the Authors for the survey.</p>
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REVIEWER	Jeanine Roeters van Lennep Erasmus MC, Rotterdam, The Netherlands
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	This manuscript is interesting and adds useful information to the field especially as it gives insight to the knowledge, awareness and preferences of primary care physicians in countries in which information about the attitude of PCPs on FH has not been published before.
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	<p>The manuscript is written in a clear style and reads nicely</p> <p>Specific comments:</p> <p>Introduction: There seems only sparse data about the prevalence of FH in Asian countries. Only one of the four references mentioned to support the statement that the prevalence of FH is between 1:200-1:500 concerns an Asian (Chinese) population. Are there more publications about the prevalence of FH in Asian populations? If not I would suggest to mention this uncertainty.</p> <p>Methods: Were the results different depending of the source how the questionnaire reached the PCP (cardiovascular conference/conference/mail lists) ?</p> <p>Results: Table 2: In the legend the term “worse” or “better” than the UK is used. Especially concerning the questions about preference I think this implies a value judgment which is misplaced.</p> <p>Discussion: The authors stress the importance of FH education programs. Could the authors elaborate what would be the most effective education program (both of lay and medical community) and also how to measure if is indeed effective.</p>
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REVIEWER	<p>Samuel S. Gidding MD Cardiology Division Head Nemours Cardiac Center A. I. DuPont Hospital for Children United States</p> <p>I have published several papers with Dr Watts. I am a consultant for RegnXbio</p>
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	<p>The authors present a survey of primary care providers in the Asia-Pacific with regard to FH. They document the low level of knowledge regarding FH in the general practice community and the variation across countries, including in comparison to the United Kingdom.</p> <p>Comments:</p> <ol style="list-style-type: none"> 1. Discussion page 9, lines 5-7: The relative risk of CVD with FH varies significantly by age. This sentence should be clearer. 2. Discussion page 10, lines 9-12: Screening does not necessarily need to be limited to a medical context. The workplace or schools could also be considered if the right flow to manage abnormal results was in place. 3. Discussion page 11 lines 13-32: It should be recognized in the current era of genetic testing in populations, about one third of those with genetically confirmed FH have LDL levels below clinical diagnosis thresholds though they also have increased CVD risk.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Professor Claudia Stefanutti, MD, PhD Institution and Country: Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre Immunohematology and Transfusion Medicine, 'Umberto I' Hospital, Department of Molecular Medicine 'Sapienza' University of Rome, Rome, ITALY Please state any competing interests: None declared

The study was aimed at assessing physicians' knowledge, awareness and preferences regarding the care of familial hypercholesterolaemia (FH) in the Asia-Pacific region, and carried out utilising a questionnaire to be anonymously completed by physicians from different countries/regions in the Asia-Pacific.

The study is original and interesting. However, it would be of interest and desirable for the Reader to provide a copy of the questionnaire to be reported as supplemental file, as the questionnaire is the principal method utilised by the Authors for the survey.

A copy of the questionnaire is available in the supplementary appendix.

Lastly, a more extensive discussion on study limitations would be desirable.

We have now added to the discussion more on study's limitations on Page 10 Line 30 to Page 11 Line 5, as well as to the Strengths and Limitations section (after the abstract).

Reviewer: 2

Reviewer Name: Jeanine Roeters van Lennep Institution and Country: Erasmus MC, Rotterdam, The Netherlands Please state any competing interests: None declared

This manuscript is interesting and adds useful information to the field especially as it gives insight to the knowledge, awareness and preferences of primary care physicians in countries in which information about the attitude of PCPs on FH has not been published before.

The manuscript is written in a clear style and reads nicely

Specific comments:

Introduction:

There seems only sparse data about the prevalence of FH in Asian countries. Only one of the four references mentioned to support the statement that the prevalence of FH is between 1:200-1:500 concerns an Asian (Chinese) population. Are there more publications about the prevalence of FH in Asian populations? If not I would suggest to mention this uncertainty.

Data on the prevalence of FH in Asian countries is sparse. The only other data on prevalence in the region are from the Hokuriku district of Japan where the prevalence is exceptionally high, owing to a historically old mutant that prevailed locally and widely over a long period of time. We have now added this reference and discussed it on Page 9, Lines 7-9.

Methods:

Were the results different depending of the source how the questionnaire reached the PCP (cardiovascular conference/conference/mail lists) ?

The mail list approach was specific to the United Kingdom. All other countries/regions administered the survey at primary care meetings and conferences. This is a limitation to the study and we have added this to the discussion; Page 11 Lines 6-8.

Results:

Table 2: In the legend the term “worse” or “better” than the UK is used. Especially concerning the questions about preference I think this implies a value judgment which is misplaced.

We have now changed this to “significantly less than” and “significantly more than”.

Discussion:

The authors stress the importance of FH education programs. Could the authors elaborate what would be the most effective education program (both of lay and medical community) and also how to measure if it is indeed effective.

We have added education approaches that could be useful and how to measure the effectiveness on Page 11, Lines 20-27 – “Education programs in medical schools and accredited courses with continuing professional development points could be useful; problem based learning is particularly effective. General media (newspaper, health magazines, television and radio), social media, and patient support groups can be utilised to educate the lay community. The effectiveness of teaching and learning programs require prospective audits and ultimately their impact needs to be gauged with defined outcomes in practices, such as the number of new cases of FH detected, commenced on statins and the proportion of all cases achieving guideline recommended LDL-targets.”

Reviewer: 3

Reviewer Name: Samuel S. Gidding MD Cardiology Division Head Nemours Cardiac Center

Institution and Country: A. I. DuPont Hospital for Children, United States Please state any competing

interests: I have published several papers with Dr Watts. I am a consultant for RegnXbio

The authors present a survey of primary care providers in the Asia-Pacific with regard to FH. They document the low level of knowledge regarding FH in the general practice community and the variation across countries, including in comparison to the United Kingdom.

Comments:

1. Discussion page 9, lines 5-7: The relative risk of CVD with FH varies significantly by age. This sentence should be clearer.

We have now clarified this sentence, now Page 9, Lines 9-10.

2. Discussion page 10, lines 9-12: Screening does not necessarily need to be limited to a medical context. The workplace or schools could also be considered if the right flow to manage abnormal results was in place.

We agree and have included this notion on Page 10, Lines 13-15 – “Screening may also be undertaken in a non-medical context such as workplace and schools; this option was not specifically enquired for in the present survey.”

3. Discussion page 11 lines 13-32: It should be recognized in the current era of genetic testing in populations, about one third of those with genetically confirmed FH have LDL levels below clinical diagnosis thresholds though they also have increased CVD risk.

We agree with this and have added on Page 12, Lines 14-17 – “Recent evidence from the US indicating that pathogenic mutations in the LDLr pathway predicts CAD across a wide spectrum of plasma LDL-C levels implies that further enquiries could focus on the use of and value of genetic testing in diagnosing and stratifying risk among patients with FH in the Asia-Pacific region.”

VERSION 2 – REVIEW

REVIEWER	Jeanine Roeters van Lennep Erasmus MC Rotterdam, The Netherlands
REVIEW RETURNED	04-Jul-2017

GENERAL COMMENTS	The authors have answered all questions raised by the reviewers sufficiently.
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REVIEWER	Samuel Gidding A I DuPont Hospital for Children Wilmington, DE USA
REVIEW RETURNED	10-Jul-2017

GENERAL COMMENTS	Satisfactory response to prior critique
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