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Complete List of Authors:	Pang, Jing; University of Western Australia, School of Medicine, Faculty of Health and Medical Sciences Hu, Miao; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Lin, Jie; Beijing Anzhen Hospital, Capital Medical University - Beijing Institute of Heart, Lung and Blood Vessel Diseases Miida, Takashi; Juntendo University, Department of Clinical Laboratory Medicine, Graduate School of Medicine Nawawi, Hapizah; Universiti Teknologi MARA, Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Disciplines of Chemical Pathology and Primary Care, Faculty of Medicine Park, Jeong Euy; Sungkyunkwan University School of Medicine, Division of Cardiology, Samsung Medical Center Wu, Xue; Beijing Anzhen Hospital, Capital Medical University - Beijing Institute of Heart, Lung and Blood Vessel Diseases Ramli, Anis Safura; Universiti Teknologi MARA, Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Disciplines of Chemical Pathology and Primary Care, Faculty of Medicine Kim, Ngoc Thanh; Hanoi Medical University; Vietnam National Heart Institute, Bach Mai Hospital Kwok, See; University of Manchester, Institute of Human Development; The Old St Mary's Hospital, Cardiovascular Trials Unit, Central Manchester University Hospital NHS Foundation Trust Gonzales, Lourdes Ella; UP-Philippine General Hospital, Section of Preventive Cardiology, Department of Cardiology Su, Ta-Chen; National Taiwan University Hospital, Department of Internal Medicine and Cardiovascular Center Truong, Thanh Huong; Hanoi Medical University; Vietnam National Heart Institute, Bach Mai Hospital Soran , H ; Cardiovascular Research Group, University of Manchester; Cardiovascular Trials Unit, Central Manchester University Hospitals Yamashita, Shizuya; Osaka University Graduate School of Medicine, Departments of Cardiovascular Medicine and Community; Rinku General Medical Center Tomlinson, Brian; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Watts, Gerald; University of Western Australia, School of Medicine, Faculty of Health and Medical Sciences; Royal Perth Hospital, Lipid Disorders Clinic, Department of Cardiology

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Primary Care Physicians' Knowledge, Awareness and Preferences regarding the care of Familial Hypercholesterolemia in the Asia-Pacific region: The "Ten Countries Study"

Jing Pang[1], Miao Hu[2], Jie Lin[3], Takashi Miida[4], Hapizah M Nawawi[5], Jeong Euy Park[6], Xue Wu[3], Anis S Ramli[5], Ngoc Thanh Kim[7,8], See Kwok[9,10], Lourdes E Gonzalez-Santos[11], Ta-Chen Su[12], Thanh Huong Truong[7,8], Handrean Soran[10], Shizuya Yamashita[13,14], Brian Tomlinson[2] and Gerald F Watts[1,15]

[1]School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia
[2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong SAR
[3]Department of Atherosclerosis, Beijing Anzhen Hospital, Capital Medical University - Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China
[4]Department of Clinical Laboratory Medicine, Graduate School of Medicine, Juntendo University, Tokyo, Japan
[5]Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Disciplines of Chemical Pathology and Primary Care, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia
[6]Division of Cardiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[7]Hanoi Medical University, Hanoi, Vietnam
[8]Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam.
[9]University of Manchester, Institute of Human Development, Manchester, United Kingdom
[10]Cardiovascular Trials Unit, The Old St Mary's Hospital, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom
[11]Section of Preventive Cardiology, Department of Cardiology, UP-Philippine General Hospital, Manila, Philippines
[12]Department of Internal Medicine and Cardiovascular Center, National Taiwan University Hospital, Taipei, Taiwan
[13]Departments of Cardiovascular Medicine and Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[14]Rinku General Medical Center, Osaka, Japan
[15]Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia

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Corresponding author:
Professor Gerald F Watts
Postal address: GPO Box X2213 Perth WA 6847 Australia
Phone: +61 8 9224 0245
Email: gerald.watts@uwa.edu.au

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ABSTRACT

Objective: To determine physicians' knowledge, awareness and preferences regarding the care of familial hypercholesterolaemia (FH) in the Asia-Pacific region.

Setting: A formal questionnaire was anonymously completed by physicians from different countries/regions in the Asia-Pacific. The survey sought responses relating to general familiarity, awareness of management guidelines, identification (clinical characteristics and lipid profile), prevalence and inheritance, extent of elevation in risk of cardiovascular disease (CVD), and practice on screening and treatment.

Participants: Practising community physicians from Australia, Japan, Malaysia, South Korea, Philippines, Hong Kong, China, Vietnam and Taiwan were recruited to complete the questionnaire, with the United Kingdom as the international benchmark.

Primary outcome: An assessment and comparison of the knowledge, awareness and preferences of FH among physicians in ten different countries/regions.

Results: 1,078 physicians completed the questionnaire from the Asia-Pacific region; only 34% considered themselves to be familiar with FH. 72% correctly described FH and 65% identified the typical lipid profile, with a higher proportion of physicians from Japan and China selecting the correct FH definition and lipid profile compared with those from Vietnam and Philippines. However, less than half of the physician were aware of national or international management guidelines; this was significantly worse than physicians from the United Kingdom (35% vs 61%, p<0.001). Knowledge of prevalence (24%), inheritability (41%), and CVD risk (9%) of FH were also suboptimal. The majority of the physicians considered laboratory interpretative commenting as being useful (81%) and statin therapy as an appropriate cholesterol-lowering therapy (89%) for FH management.

Conclusions: The study identified important gaps, which are readily addressable, in the awareness and knowledge of FH among physicians in the region. Implementation of country-specific guidelines and extensive work in FH education and awareness programs are imperative to improve the care of FH in the region.

Strengths and limitations of this study

- The study is a large-scale multi-national survey assessing FH knowledge and management gaps across ten different countries/regions, with over 1000 physicians completing the questionnaire
- Important deficits and gaps in knowledge and management of FH were identified in the region
- The self-selected group that responded to the questionnaire may reflect those with more interest and knowledge in lipid disorders, so that knowledge and management gaps may in reality be worse.
- Since the survey was conducted anonymously, there was no recorded information on non-responders.

INTRODUCTION

Familial hypercholesterolaemia (FH) is characterised by elevated low-density lipoprotein cholesterol (LDL-C) levels owing to mutations in the low-density lipoprotein receptor (LDLr) pathway. FH is the most common inherited lipid disorder that accelerates atherosclerotic cardiovascular disease (CVD). However, the majority of people with FH are undiagnosed and undertreated[1]. FH is a public health problem throughout the world. The prevalence of heterozygous FH is estimated to be 1 in 200 to 1 in 500[2-6] in unselected community populations, with an estimated 3.6 million individuals in the Asia-Pacific region alone[7] and less than 1% are considered to be formally diagnosed in the region[8 9]. FH healthcare in the region leaves much to be desired.

Primary care physicians (PCPs) or family doctors are well placed in the community to opportunistically detect FH[10 11] and need to be involved in the care of these patients. The role of primary care in the care of FH has not been adequately defined and our preliminary data suggest a significant shortfall in knowledge and awareness among family doctors[7 12]. As part of the "Ten Countries Study"[13], we investigated several aspects of the knowledge, awareness and preferences of FH among PCPs in ten countries/regions, primarily in the Asia-Pacific Region.

METHODS

The methodology for the present study has been previously described as part of the overarching "Ten Countries Study"[13], a project investigating several aspects of the care of FH. The United Kingdom, a country with a highly developed healthcare system and a sophisticated guideline for the care of FH developed by the National Institute for Health and Care Excellence (NICE)[14], was included to provide the international benchmark.

In brief, a formal questionnaire was offered to PCPs via cardiovascular education sessions, conferences and/or mail lists from the country-equivalent Royal Colleges. Language-specific versions of the questionnaire were developed from the English-language version via standardised back-translation techniques and the aid of bilingual translators. The survey inquired about the following aspects of FH: familiarity with the condition, awareness of national and international guidelines for

FH; the clinical description of FH; identification of the typical lipid profile; prevalence and inheritance of FH; extent of elevation in risk of CVD, whether the diagnosis requires genetic confirmation; methods for alerting PCPs about the possibility of FH; type of health professional best placed to detect FH; number of patients with FH currently being treated; specific treatments; knowledge and practices concerning family screening; treatment and referral practices regarding patients with severely elevated cholesterol. Demographic data were also recorded.

Between March 2014 and August 2016, the survey was completed voluntarily and anonymously among physicians in nine countries and/or regions in Asia-Pacific (Australia, Japan, Malaysia, South Korea, Philippines, Hong Kong, China, Vietnam and Taiwan), as well as the United Kingdom[15]. Results from the PCPs surveyed in the United Kingdom and the details of the survey have been published[15]. Data were analysed using STATA 12 (StataCorp). Chi-squared tests were performed to compare the Asia-Pacific PCPs to the United Kingdom. The survey responses from each country/region was compared to the United Kingdom, as the reference group. The differences were investigated using logistic regression analyses. Significance was defined at the 5% level.

RESULTS

1,335 physicians completed the questionnaire; 257 physicians declared themselves to be specialist physicians and were excluded from the study. 1,078 PCPs from Australia (n=151), Japan (n=197), Malaysia (n=219), South Korea (n=97), Philippines (n=62), Hong Kong (n=59), China (n=118), Vietnam (n=137) and Taiwan (n=38) were included in the study. 54% of the respondents were male. There were a greater proportion of male respondents from Japan (84%) and South Korea (81%) compared with Malaysia (24%) and the Philippines (37%). Overall, practice location was spread over urban/metropolitan (63%), suburban/outer metropolitan (17%) and rural (20%) areas. Respondents from Hong Kong and Taiwan were all based in urban/metropolitan areas, possibly owing to the small size of their regions (<40,000km^2). Table 1 details the demographics of the PCPs from the individual countries/regions and their knowledge, awareness and preferences regarding FH. 100 PCPs from the United Kingdom were the comparator group.

A third of PCPs from Asia-Pacific rated their familiarity with FH as above average (>4, from a scale of 1 to 7). Although self-perceived familiarity with FH was not significantly different among most countries (except lower in Japan and China) and the United Kingdom, awareness of FH guidelines was significantly lower in Asia-Pacific compared with the United Kingdom (35% vs 61%, p<0.001). Similarly, the awareness of lipid specialists for referral or medical advice was significantly lower in Asia-Pacific compared with the United Kingdom (35% vs 50%, p=0.003); only Australian and Taiwanese PCPs were comparably aware. Regarding the knowledge of FH, PCPs from the United Kingdom were significantly better at selecting the correct FH description (89% vs 72%, p=0.001) compared with the Asia-Pacific PCPs.

In spite of the lower self-perceived familiarity with FH, Japanese and Chinese physicians were significantly better at identifying the correct FH lipid profile, compared with the United Kingdom. The response to questions concerning the prevalence, inheritance and CVD risk of FH were suboptimal in all countries/regions, and particularly in China and Vietnam. Half of the PCPs correctly identified that genetic testing was not required to accurately diagnose FH. The majority of PCPs selected statins as the best pharmacotherapy to best treat hypercholesterolaemia, with a significantly lower proportion of PCPs selecting this from Japan and Vietnam, compared with the United Kingdom. Half of the PCPs selected the combination of statin and ezetimibe to treat severe hypercholesterolemia, with a significantly higher proportion of PCPs selecting this from Australia, South Korea and China, compared with the United Kingdom.

Concerning practices relating to FH, PCPs from the Asia-Pacific region and the United Kingdom were equally likely to screen patients with premature CAD for their family history of CVD. Of PCPs who had FH patients under their care, 66% from Asia-Pacific and 73% the United Kingdom responded that they would perform routine screening of their family members and there was no significant difference. However, Japanese PCPs caring for FH patients were the lowest who would undertake family screening among the countries/regions. The most prevalent age for screening young people in a kindred with FH was selected at 13-18 years. Although awareness of lipid specialists were suboptimal, in PCPs that were aware of lipid specialists, only 56% had referred FH patients to a lipid specialist in the Asia-Pacific region,

compared with 72% in the United Kingdom which was significantly higher (p=0.028); Japan, Philippines, Vietnam and Malaysia were particularly low.

The majority of PCPs from the United Kingdom (82%) selected themselves as the most effective health care provider for the early detection of FH. However, the response was highly disparate in the Asia-Pacific region, with only 8% of responses from China and 23% from Vietnam identifying PCPs as the preferred health care provider for the early detection of FH. By contrast, 92% of from Malaysia and 80% from Australia, selected PCPs (Table 1). Overall, cardiologists (38%), lipid specialists (36%) and endocrinologists (10%) were also selected by the PCPs from the Asia-Pacific. However, PCPs did not consider that there was a significant role for paediatricians, obstetricians/gynaecologists and/or nurses with cardiac training in the care of FH. The majority of PCPs selected an interpretive laboratory comment on lipid test report results as being useful in detecting FH.

DISCUSSION

Recent knowledge of the population frequency of FH suggests that it can be viewed as a public health problem. Strategies for improving early diagnosis and care of FH in the community requires adequate knowledge and appropriate practices concerning this condition. This study is the first survey to demonstrate significant gaps in knowledge and awareness of FH across several countries/regions in the Asia-Pacific and to identify important areas of deficit.

In the present study, the lack of awareness of guidelines and lipid specialists can be related to the lack of country-specific guidelines[16] on FH and the lack of physicians specifically trained and practicing as lipid experts in the region. Although the UK performed significantly better on these questions compared with the countries/regions in the Asia-Pacific, the results were still suboptimal. 39% were unaware of FH guidelines despite the fact that the NICE guidelines for identifying FH were released 7-8 years ago, and 50% were not aware of a lipid specialist in spite of the efforts from Heart UK in mapping specialist lipid clinics and establishing an FH Intelligence Network. Lack of awareness of clinical services for lipid disorders may be because specialist services do not exist in their geographical area, particularly for PCPs practising in suburban and rural regions, which constituted 43% of the PCPs surveyed.

The PCPs were generally able to correctly define FH. However, knowledge of FH prevalence, heritability and risk of CVD were suboptimal. Three quarters of PCPs in the present study were not aware of the theoretical prevalence of FH of 1:500 (with 42% selecting 'don't know') and 91% were not aware of the >20-fold risk of CVD in untreated FH[17] (with 30% selecting 'don't know'). However, as demonstrated by recent studies, heterozygous FH may be more common than 1:500[2-6] and CVD risk could be ~10-fold[18], varying with age. Taking this into account, 45% of respondents identified the prevalence as between 1:100-1:1000 and 60% selected CVD risk to be 5-20 times greater. Although still suboptimal, this at least indicates an understanding that the risk of CVD is high among patients with FH.

Knowledge and familiarity with lipid-lowering treatment was reassuring; most PCPs identified statins to best treat hypercholesterolaemia. A lower proportion of physicians from Japan and Vietnam selected statins, which may relate to the availability of alternative medication (eg. probucol) and the lack of access to statins in some regions. Owing to the severity of hypercholesterolaemia, most FH patients will require additional therapy to reach treatment goals[1]. PCPs from China, South Korea and Australia were particularly good at selecting combination statin and ezetimibe therapy for treating severe hypercholestolaemia. By contrast, selection of combination statin and ezetimibe therapy in Vietnam was low and this may relate to the lack of general access to pharmacotherapies.

PCPs are critical in achieving long-term treatment adherence and have a key role in recognising family history of premature CAD. An accurate family history is integral to both CVD risk assessment and the diagnosis of FH. Encouragingly, 90% of PCPs would take a detailed family history in patients with premature CAD. However, there were gaps in cascade screening of close relatives, especially in Japan. Although the European guidelines suggest screening of children in an FH kindred from the age of 5 years[19] and the NICE guidelines recommend screening children between 2-10 years, PCPs in the Asia-Pacific region considered that testing between 13-18 years of age was a more appropriate practice. Studies on cholesterol screening in US paediatricians raised concerns regarding conflicting guidelines on lipid screening and treatment practices[20] and half of the paediatricians were opposed to the use of lipid-lowering therapies in children[20 21].

Differences in the choice of healthcare professional perceived as best suited for managing FH and family screening among the countries/regions may reflect different healthcare systems. In particular, 83% of Chinese PCPs considered that lipid specialists were better suited to manage FH. There was the view that cardiologists are well positioned to identify index cases with FH presenting with coronary events[22 23]. Similarly, endocrinologists were considered well placed to identify FH in a secondary prevention setting. Overall, respondents in the present study considered that PCPs were best situated to identify FH in the primary prevention setting. Few considered that there was a significant role for nurses. This differs from the Netherlands[24] where screening programs have been conducted by nursing and/or allied health staff. Further exploration of health services and systems are warranted to optimise country-specific clinical service models and integration of care[1].

The majority of PCPs in the present study thought that interpretative commenting attached to the reports on lipid profiles in people at high-risk of FH would be useful. This mode of alerting could play a role in the detection and management of FH[25]. Electronic screening tools to retrospectively identfiy FH in general practices could also be useful; some preliminary work from the United Kingdom and Australia has demonstrated the potential to increase identification of FH via this method[26-28]. Other methods such as screening via the laboratory[29 30] and improving communication between the requesting physican and the chemical pathologist[31] may also be useful. Implementing these in service mode will require an integrated collaborative approach with local laboratories, pathologists and treating physcians.

Increased lipoprotein(a) [Lp(a)], smoking, hypertension and diabetes are all known to compound CVD risk and are predictors of CAD in FH[32-39]. A limitation of the present survey was that CVD risk factors were not explored, particularly with the increasing prevalence of risk factors in Asia[40]. Another limitation of the study may be the self-selected group that responded to the questionnaire and may reflect those with more interest and knowledge in lipid disorders. Since the survey was conducted anonymously, there was no recorded information on non-responders.

Similar surveys have been undertaken in PCPs[12] and pharmacists[41] in Western Australia, cardiologists in the US[23] and physicians in India[42], as well as a pilot study among physicians in Japan, South Korea, Taiwan[7]. Knowledge shortfalls were

comparable, with underestimations of prevalence, hereditability and CVD risk. A recent study by *Schofield* et al[43] assessed FH knowledge among a diverse group of health care professionals (including nurses and pharmacists in the United Kingdom and demonstrated knowledge gaps in FH prevalence, diagnostic criteria and treatment options. In a smaller cohort (n=35) of health care professionals that completed a second survey following an FH education session, all aspects of FH knowledge was improved. *Bell* et al[44] have also shown that with direct education, PCPs are able to accurately assess FH. This emphasises the important of investing in FH education programs[45]. A global initiative, the European Atherosclerosis Society FH Studies Collaboration was launched with aims to disseminate information to empower the medical and lay community to seek changes to improve the care of patients and families with FH[46].

Screening programs in the region have been communicated by Singapore[47] and Hong Kong[48]. Owing to high population densities in the region, family cascade screening after the detection of an index case with FH could be particularly efficient and cost-effective. However, specific diagnostic criteria and guidelines in the region are only available from Australia[49], Japan[50] and South Korea[51]. The Australasian model of care is a comprehensive clinical guideline encompassing elements of index case detection, diagnosis and assessment, management, cascade screening, genetic testing and the organisation of clinical services[49]. The Japanese criteria are based on the detection of tendon xanthomata[50], which may only be present in ~30% of FH patients and particularly uncommon in the young[52], and hence may have low sensitivity in screening and detecting FH. A study from South Korea demonstrated the lack of detection power with all conventional clinical criteria and suggested an LDL-C cut-off of 225mg/dL (~5.8mmol/L)[51]. However, the LDL-C cut-off was derived from a biased sample of patients with existing hypercholesterolemia. The lack of country-specific criteria may contribute to the lack of active screening programs employed in the region and the cost of genetic testing in the community beyond research studies is not justified. FH research in the region is highly warranted; the mutation spectrum of FH is different from the European spectrum[53] and the mean cholesterol concentrations in most Asian countries are lower compared with Western countries[16].

The integrated international guidance on FH[1], endorsed by the Asian-Pacific Society of Atherosclerosis and Vascular Disease[54], provides a foundation for developing country-specific guidelines, services and models of care. The principles are similar, but require the development of country-specific recommendations to screen, diagnose and treat FH, as well as strategies for long-term adherence and goal attainment[55]. Country-specific challenges in developing screening programs may relate to their healthcare systems, as well as diverse cultures, political systems and economies[56 57] in the region. Challenges in treatment and management include the tolerability of statins, its availability and affordability[58], and its acceptability against the popularity of complementary and alternative medicines[59 60]. The FH "Ten Countries Study" group is the first collaborative effort in the region focusing specifically on FH and should hopefully see the extension of the series of studies, including the present study, into the translation and transference of the research findings to country-specific models of cares[13].

CONCLUSION

The present study identified substantial deficits in FH knowledge and awareness among physicians in the Asia-Pacific region, in particular, awareness of guidelines and knowledge of diagnostic features of FH. Knowledge of FH hereditability, prevalence and CVD risk were also suboptimal. Major treatment gaps were identified in Vietnam and gaps in family screening were noted in Japan. However, through extensive FH education, awareness programs and implementation of country-specific guidelines, these gaps can be addressed to accelerate the pace of FH diagnosis and treatment. Similar surveys are required in specialists practicing coronary prevention in the region. A potentially effective method of standardising care across countries is participation in an international registry[61].

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Competing interests

All authors have completed the Unified Competing Interest form. TM reports grants from JSPS during the conduct of the study; grants from Denka-Seiken, Shino-test, MSD and Otsuka outside the submitted work; and honoraria from Sanofi, Astellas-Amgen, Astra Zeneka, Otsuka, Takeda, Kowa, Denka-Seiken, Sekisui-Medical, Kyowa Medex and Wako. HS reports research grants from Alexion, Amgen, MSD and Pfizer; and personal fees and education grants from Aegerion, Amgen, Janssen Cilag Ltd, MSD, Pfizer,Novo Nordisk and Sanofi. SY reports grants and personal fees from Kowa, Otsuka, Shionogi, Bayer Yakuhin, MSD, Takeda, Sanwa Kagaku Kenkyusho, Astellas, Daiichi-Sankyo, Astra Zeneca and Kaken; grants from Nippon Boehringer Ingelheim, Kyowa Medex, Mochida, Hayashibara, Teijin, Kissei and National Institute of Biomedical Innovation; and personal fees from Medical Review Co., Skylight Biotech, Pfizer, Bristol-Meyers, Astellas-Amgen, Sanofi, Agerion and Toa Eiyou, outside the submitted work. In addition, SY has two pending patents, Fujirebio and Kyowa Medex. BT reports grants and personal fees from Amgen; grants from AstraZeneca, Merk Sharp & Dohme, Novartis, Pfizer and Roche; personal fees from Merck Serono and Sanofi, outside the submitted work. GFW reports grants from Sanofi /Regeneron during the conduct of the study; grants and personal fees from Sanofi /Regeneron and Amgen; personal fees from Gemphire and

Kowa, outside the submitted work. JP, THT, NTK, ASR, JEP, LGS, JL, XW, MH, HMN and SK have nothing to disclose.

Contributorship statement

JP designed data collection tools, implemented the study for the all countries, monitored data collection, cleaned and analysed the data, and drafted and revised the paper. MH and BT implemented the study in Hong Kong and revised the draft paper. JL and XW implemented the study in China and revised the draft paper. TM and SY implemented the study in Japan and revised the draft paper. HMN and ASR implemented the study in Malaysia and revised the draft paper. JEP implemented the study in Vietnam and revised the draft paper. THT and NTK implemented the study in Vietnam and revised the draft paper. HS and SK implemented the study in the United Kingdom and revised the draft paper. LGS implemented the study in the Philippines and revised the draft paper. TS implemented the study in Taiwan and revised the draft paper. GFW initiated the collaborative project, designed data collection tools, implemented the study for the all countries, advised the statistical analysis plan and revised the paper.

Transparency declaration

JP affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Date sharing statement

No additional data available. Extra details on data presented in the current study is available by emailing jing.pang@uwa.edu.au.

1 **Table 1: Summary of PCP's demographics and responses to questions (%) about awareness, knowledge, practices and preferences regarding FH in "Ten Countries".**

Country/Region	Australia	Japan	Malaysia	South Korea	Philippines	Hong Kong	China	Vietnam	Taiwan	United Kingdom[15]
Number of PCPs	**151**	**197**	**219**	**97**	**62**	**59**	**118**	**137**	**38**	**100**
DEMOGRAPHICS										
Male	62%	84%	24%	81%	37%	53%	42%	46%	74%	42%
Urban/Metropolitan	52%	49%	63%	82%	63%	100%	82%	40%	100%	47%
Suburban/Outer metropolitan	33%	30%	0%	14%	15%	0%	18%	27%	0%	44%
Rural	16%	21%	37%	4%	23%	0%	0%	33%	0%	9%
AWARENESS										
Familiarity of FH rated as above average	32%	23%	38%	28%	34%	50%	23%	49%	47%	39%
Awareness about FH guidelines	36%	47%	35%	34%	N/A	43%	8%	28%	53%	61%
Awareness about lipid specialists	51%	33%	34%	30%	31%	40%	12%	39%	57%	50%
KNOWLEDGE										
Correctly described FH	72%	77%	86%	51%	73%	62%	75%	65%	60%	89%
Correctly identified lipid profile	59%	85%	65%	57%	48%	51%	85%	45%	61%	74%
Correctly identified prevalence of FH in the community	26%	41%	24%	19%	16%	11%	17%	14%	30%	30%
Correctly identified the transmission rate of FH to first degree relatives	44%	40%	49%	42%	37%	49%	36%	26%	61%	51%
Correctly identified the CVD risk in untreated FH patients	14%	13%	9%	8%	10%	7%	4%	2%	5%	14%
Correctly identified that genetic testing was not required to accurately diagnose FH	50%	52%	47%	64%	68%	38%	38%	58%	24%	52%
Selected statins to best treat hypercholesterolemia	89%	85%	96%	90%	95%	93%	95%	75%	95%	94%
Selected a combination of statin and ezetimibe to treat severe hypercholesterolemia	64%	48%	56%	70%	48%	49%	77%	31%	63%	50%
PRACTICE										
Screened patients with premature CAD for family history	93%	83%	95%	89%	92%	95%	94%	85%	95%	90%
Performed routine family screening of patients with FH (if there were FH patients under their care)	86%	30%	82%	50%	53%	90%	47%	83%	77%	73%
The most prevalent age for screening young people in a kindred with FH was 13-18 years, which was selected by	52%	18%	52%	54%	52%	48%	16%	33%	20%	45%
Have referred FH patients to a lipid specialists (if aware of lipid specialist)	66%	26%	52%	57%	32%	86%	86%	49%	100%	72%
PREFERENCE										
Selected PCPs as the most effective health care provider for the early detection of FH	80%	45%	92%	71%	58%	76%	8%	23%	50%	82%
Selected interpretive commenting on lipid profiles to highlight patients at risk of FH	89%	57%	92%	84%	92%	85%	86%	72%	89%	88%

1

Table 2: Comparison of PCP's responses to questions about FH awareness, knowledge, practices and preferences with the United Kingdom as the reference group using logistic regression analyses; odds ratio (95% confidence interval) shown.

Country/Region	Australia	Japan	Malaysia	South Korea	Philippines	Hong Kong	China	Vietnam	Taiwan
AWARENESS									
Familiarity of FH rated as above average	0.73 (0.43-1.24)	0.47 (0.28-0.79)*	0.95 (0.58-1.55)	0.61 (0.33-1.11)	0.80 (0.41-1.55)	1.56 (0.81-3.01)	0.46 (0.25-0.83)*	1.52 (0.90-2.57)	1.41 (0.66-2.99)
Awareness about FH guidelines	0.34 (0.21-0.61)**	0.58 (0.36-0.95)*	0.35 (0.22-0.58)**	0.34 (0.19-0.61)**	N/A	0.49 (0.26-0.95)*	0.05 (0.02-0.12)**	0.25 (0.14-0.43)**	0.72 (0.34-1.53)
Awareness about lipid specialists	1.03 (0.62-1.71)	0.5 (0.30-0.82)*	0.51 (0.31-0.83)*	0.43 (0.24-0.78)*	0.44 (0.23-0.86)*	0.68 (0.35-1.31)	0.14 (0.07-0.27)**	0.64 (0.37-1.11)	1.33 (0.61-2.90)
KNOWLEDGE									
Correctly described FH	0.33 (0.16-0.68)*	0.42 (0.21-0.86)*	0.78 (0.37-1.62)	0.13 (0.06-0.28)**	0.34 (0.15-0.78)*	0.21 (0.09-0.48)**	0.38 (0.18-0.82)*	0.24 (0.12-0.50)**	0.19 (0.07-0.50)*
Correctly identified lipid profile	0.52 (0.30-0.90)*	2.06 (1.12-3.77)*	0.65 (0.38-1.10)	0.47 (0.26-0.85)*	0.33 (0.17-0.65)*	0.37 (0.18-0.65)*	2.07 (1.05-4.10)*	0.29 (0.16-0.51)**	0.55 (0.25-1.20)
Correctly identified prevalence of FH in the community	0.80 (0.46-1.41)	1.60 (0.96-2.69)	0.73 (0.43-1.25)	0.54 (0.27-1.06)	0.44 (0.20-0.99)	0.28 (0.11-0.71)*	0.49 (0.25-0.93)*	0.38 (0.20-0.73)*	0.97 (0.43-2.22)
Correctly identified the transmission rate of FH to first degree relatives	0.74 (0.44-1.23)	0.63 (0.39-1.03)	0.91 (0.56-1.48)	0.70 (0.38-1.27)	0.57 (0.30-1.08)	0.92 (0.46-1.84)	0.54 (0.31-0.93)*	0.34 (0.19-0.59)**	1.52 (0.68-3.46)
Correctly identified the CVD risk in untreated FH patients	0.97 (0.46-2.02)	0.90 (0.44-1.83)	0.59 (0.28-1.22)	0.56 (0.22-1.40)	0.66 (0.24-1.81)	0.46 (0.14-1.48)	0.28 (0.10-0.81)*	0.15 (0.04-0.52)*	0.34 (0.07-1.58)
Correctly identified that genetic testing was not required to accurately diagnose FH	0.91 (0.55-1.51)	1.00 (0.61-1.62)	0.83 (0.51-1.33)	1.63 (0.92-2.90)	1.94 (1.00-3.76)	0.56 (0.29-1.09)	0.56 (0.33-0.97)*	1.28 (0.76-2.17)	0.30 (0.13-0.96)*
Selected statins to best treat hypercholesterolemia	0.50 (0.19-1.32)	0.37 (0.15-0.92)*	1.68 (0.57-4.99)	0.56 (0.19-1.59)	1.26 (0.30-5.21)	0.88 (0.24-3.25)	1.19 (0.37-3.82)	0.19 (0.08-0.48)*	0.74 (0.18-3.14)
Selected a combination of statin and ezetimibe to treat severe hypercholesterolemia	1.75 (1.04-2.92)*	0.91 (0.56-1.48)	1.26 (0.78-2.02)	2.34 (1.31-4.21)*	0.94 (0.50-1.77)	0.97 (0.51-1.84)	3.37 (1.88-6.03)**	0.46 (0.27-0.78)*	1.71 (0.80-3.69)
PRACTICE									
Screened patients with premature CAD for family history	1.57 (0.63-3.91)	0.53 (0.25-1.23)	2.10 (0.86-5.12)	0.87 (0.35-2.15)	1.27 (0.41-3.90)	2.07 (0.55-7.86	1.76 (0.65-4.81)	0.61 (0.28-1.37)	2.00 (0.42-9.58)
Performed routine family screening of patients with FH (if there were FH patients under their care)	2.25 (0.81-6.22)	0.16 (0.06-0.40)**	1.75 (0.65-4.70)	0.38 (0.14-1.04)	0.43 (0.17-1.06)	3.38 (0.93-12.21)	0.34 (0.10-1.10)	1.88 (0.34-10.27)	1.23 (0.39-3.86)
Selected 13-18 years as most appropriate for screening young people in a kindred with FH	1.32 (0.79-2.21)	0.27 (0.16-0.47)**	1.30 (0.81-2.10)	1.42 (0.81-2.51)	1.28 (0.68-2.42)	1.12 (0.58-2.15)	0.23 (0.12-0.43)**	0.59 (0.34-1.02)	0.30 (0.12-0.75)*
Have referred FH patients to a lipid specialists (if aware of lipid specialist)	0.75 (0.34-1.64)	0.14 (0.06-0.32)**	0.42 (0.20-0.91)*	0.52 (0.20-1.37)	0.18 (0.06-0.57)*	2.33 (0.59-9.18)	2.33 (0.46-11.78)	0.37 (0.15-0.88)*	1
PREFERENCE									
Selected PCPs as the most effective health care provider for the early detection of FH	0.89 (0.46-1.69)	0.18 (0.10-0.32)**	2.61 (1.28-5.31)*	0.54 (0.28-1.06)	0.30 (0.15-0.62)*	0.71 (0.32-1.55)	0.02 (0.01-0.05)**	0.07 (0.04-0.13)**	0.22 (0.10-0.50)**
Selected interpretive commenting on lipid profiles to highlight patients at risk of FH	1.15 (0.52-2.55)	0.18 (0.09-0.35)*	1.52 (0.70-3.30)**	0.69 (0.31-1.55)	1.55 (0.52-4.65)	0.76 (0.30-1.92)	0.81 (0.37-1.79)	0.36 (0.17-0.72)*	1.16 (0.35-3.84)

*p<0.05, **p<0.001, =worse than the United Kingdom, =better than the United Kingdom.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

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	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	5-6
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6 & 15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
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	17
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
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	4 & 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
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	13

*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.

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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"

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Complete List of Authors:	Pang, Jing; University of Western Australia, School of Medicine, Faculty of Health and Medical Sciences Hu, Miao; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Lin, Jie; Beijing Anzhen Hospital, Capital Medical University - Beijing Institute of Heart, Lung and Blood Vessel Diseases Miida, Takashi; Juntendo University, Department of Clinical Laboratory Medicine, Graduate School of Medicine Nawawi, Hapizah; Universiti Teknologi MARA, Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Disciplines of Chemical Pathology and Primary Care, Faculty of Medicine Park, Jeong Euy; Sungkyunkwan University School of Medicine, Division of Cardiology, Samsung Medical Center Wu, Xue; Beijing Anzhen Hospital, Capital Medical University - Beijing Institute of Heart, Lung and Blood Vessel Diseases Ramli, Anis Safura; Universiti Teknologi MARA, Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Disciplines of Chemical Pathology and Primary Care, Faculty of Medicine Kim, Ngoc Thanh; Hanoi Medical University; Vietnam National Heart Institute, Bach Mai Hospital Kwok, See; University of Manchester, Institute of Human Development; The Old St Mary's Hospital, Cardiovascular Trials Unit, Central Manchester University Hospital NHS Foundation Trust Gonzales, Lourdes Ella; UP-Philippine General Hospital, Section of Preventive Cardiology, Department of Cardiology Su, Ta-Chen; National Taiwan University Hospital, Department of Internal Medicine and Cardiovascular Center Truong, Thanh Huong; Hanoi Medical University; Vietnam National Heart Institute, Bach Mai Hospital Soran , H ; Cardiovascular Research Group, University of Manchester; Cardiovascular Trials Unit, Central Manchester University Hospitals Yamashita, Shizuya; Osaka University Graduate School of Medicine, Departments of Cardiovascular Medicine and Community; Rinku General Medical Center Tomlinson, Brian; The Chinese University of Hong Kong, Department of Medicine and Therapeutics Watts, Gerald; University of Western Australia, School of Medicine, Faculty

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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"

Jing Pang[1], Miao Hu[2], Jie Lin[3], Takashi Miida[4], Hapizah M Nawawi[5], Jeong Euy Park[6], Xue Wu[3], Anis S Ramli[5], Ngoc Thanh Kim[7,8], See Kwok[9,10], Lourdes E Gonzalez-Santos[11], Ta-Chen Su[12], Thanh Huong Truong[7,8], Handrean Soran[10], Shizuya Yamashita[13,14], Brian Tomlinson[2] and Gerald F Watts[1,15]

[1]School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia
[2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong SAR
[3]Department of Atherosclerosis, Beijing Anzhen Hospital, Capital Medical University - Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China
[4]Department of Clinical Laboratory Medicine, Graduate School of Medicine, Juntendo University, Tokyo, Japan
[5]Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Disciplines of Chemical Pathology and Primary Care, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia
[6]Division of Cardiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[7]Hanoi Medical University, Hanoi, Vietnam
[8]Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam.
[9]University of Manchester, Institute of Human Development, Manchester, United Kingdom
[10]Cardiovascular Trials Unit, The Old St Mary's Hospital, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom
[11]Section of Preventive Cardiology, Department of Cardiology, UP-Philippine General Hospital, Manila, Philippines
[12]Department of Internal Medicine and Cardiovascular Center, National Taiwan University Hospital, Taipei, Taiwan
[13]Departments of Cardiovascular Medicine and Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[14]Rinku General Medical Center, Osaka, Japan
[15]Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia

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Corresponding author:
Professor Gerald F Watts
Postal address: GPO Box X2213 Perth WA 6847 Australia
Phone: +61 8 9224 0245
Email: gerald.watts@uwa.edu.au

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ABSTRACT

Objective: To determine physicians' knowledge, awareness and preferences regarding the care of familial hypercholesterolaemia (FH) in the Asia-Pacific region.

Setting: A formal questionnaire was anonymously completed by physicians from different countries/regions in the Asia-Pacific. The survey sought responses relating to general familiarity, awareness of management guidelines, identification (clinical characteristics and lipid profile), prevalence and inheritance, extent of elevation in risk of cardiovascular disease (CVD), and practice on screening and treatment.

Participants: Practising community physicians from Australia, Japan, Malaysia, South Korea, Philippines, Hong Kong, China, Vietnam and Taiwan were recruited to complete the questionnaire, with the United Kingdom as the international benchmark.

Primary outcome: An assessment and comparison of the knowledge, awareness and preferences of FH among physicians in ten different countries/regions.

Results: 1,078 physicians completed the questionnaire from the Asia-Pacific region; only 34% considered themselves to be familiar with FH. 72% correctly described FH and 65% identified the typical lipid profile, with a higher proportion of physicians from Japan and China selecting the correct FH definition and lipid profile compared with those from Vietnam and Philippines. However, less than half of the physician were aware of national or international management guidelines; this was significantly worse than physicians from the United Kingdom (35% vs 61%, p<0.001). Knowledge of prevalence (24%), inheritability (41%), and CVD risk (9%) of FH were also suboptimal. The majority of the physicians considered laboratory interpretative commenting as being useful (81%) and statin therapy as an appropriate cholesterol-lowering therapy (89%) for FH management.

Conclusions: The study identified important gaps, which are readily addressable, in the awareness and knowledge of FH among physicians in the region. Implementation of country-specific guidelines and extensive work in FH education and awareness programs are imperative to improve the care of FH in the region.

Strengths and limitations of this study

- The study is a large-scale multi-national survey assessing FH knowledge and management gaps across ten different countries/regions, with over 1000 physicians completing the questionnaire.
- The standardised questionnaire has been previously tested and employed in primary care in Australia and the United Kingdom.
- The self-selected group that responded to the questionnaire may reflect those with more interest and knowledge in lipid disorders.
- Since the survey was conducted anonymously, there was no specific information of responders and non-responders.
- The questionnaire employed did not cover all aspects of the care of FH, such as use of genetic testing and assessment of other cardiovascular risk factors.
- The analysis assumed that the primary care physicians from the United Kingdom were the gold standard respondents.

INTRODUCTION

Familial hypercholesterolaemia (FH) is characterised by elevated low-density lipoprotein cholesterol (LDL-C) levels owing to mutations in the low-density lipoprotein receptor (LDLr) pathway. FH is the most common inherited lipid disorder that accelerates atherosclerotic cardiovascular disease (CVD). However, the majority of people with FH are undiagnosed and undertreated[1]. FH is a public health problem throughout the world. The prevalence of heterozygous FH is estimated to be 1 in 200 to 1 in 500[2-6] in unselected community populations, with an estimated 3.6 million individuals in the Asia-Pacific region alone[7] and less than 1% are considered to be formally diagnosed in the region[8 9]. FH healthcare in the region leaves much to be desired.

Primary care physicians (PCPs) or family doctors are well placed in the community to opportunistically detect FH[10 11] and need to be involved in the care of these patients. The role of primary care in the care of FH has not been adequately defined and our preliminary data suggest a significant shortfall in knowledge and awareness among family doctors[7 12]. As part of the "Ten Countries Study"[13], we investigated several aspects of the knowledge, awareness and preferences of FH among PCPs in ten countries/regions, primarily in the Asia-Pacific Region.

METHODS

The methodology for the present study has been previously described as part of the overarching "Ten Countries Study"[13], a project investigating several aspects of the care of FH. The United Kingdom, a country with a highly developed healthcare system and a sophisticated guideline for the care of FH developed by the National Institute for Health and Care Excellence (NICE)[14], was included to provide the international benchmark. Since this was an anonymous quality assurance enquiry into clinical practice, formal ethics approval was not required and this was verified by the local ethics committee.

In brief, a formal questionnaire was offered to PCPs via cardiovascular education sessions, conferences and/or mail lists from the country-equivalent Royal Colleges. Language-specific versions of the questionnaire were developed from the English-language version via standardised back-translation techniques and the aid of

bilingual translators. The survey inquired about the following aspects of FH: familiarity with the condition, awareness of national and international guidelines for FH; the clinical description of FH; identification of the typical lipid profile; prevalence and inheritance of FH; extent of elevation in risk of CVD, whether the diagnosis requires genetic confirmation; methods for alerting PCPs about the possibility of FH; type of health professional best placed to detect FH; number of patients with FH currently being treated; specific treatments; knowledge and practices concerning family screening; treatment and referral practices regarding patients with severely elevated cholesterol. Demographic data were also recorded.

Between March 2014 and August 2016, the survey was completed voluntarily and anonymously among physicians in nine countries and/or regions in Asia-Pacific (Australia, Japan, Malaysia, South Korea, Philippines, Hong Kong, China, Vietnam and Taiwan), as well as the United Kingdom[15]. Results from the PCPs surveyed in the United Kingdom have been published[15]; the details of the survey are available in the supplementary appendix. Data were analysed using STATA 12 (StataCorp). Chi-squared tests were performed to compare the Asia-Pacific PCPs to the United Kingdom. The survey responses from each country/region was compared to the United Kingdom, as the reference group. The differences were investigated using logistic regression analyses. Significance was defined at the 5% level.

RESULTS

1,335 physicians completed the questionnaire; 257 physicians declared themselves to be specialist physicians and were excluded from the study. 1,078 PCPs from Australia (n=151), Japan (n=197), Malaysia (n=219), South Korea (n=97), Philippines (n=62), Hong Kong (n=59), China (n=118), Vietnam (n=137) and Taiwan (n=38) were included in the study. 54% of the respondents were male. There were a greater proportion of male respondents from Japan (84%) and South Korea (81%) compared with Malaysia (24%) and the Philippines (37%). Overall, practice location was spread over urban/metropolitan (63%), suburban/outer metropolitan (17%) and rural (20%) areas. Respondents from Hong Kong and Taiwan were all based in urban/metropolitan areas, possibly owing to the small size of their regions (<40,000km^2). Table 1 details the demographics of the PCPs from the individual

countries/regions and their knowledge, awareness and preferences regarding FH. 100 PCPs from the United Kingdom were the comparator group.

A third of PCPs from Asia-Pacific rated their familiarity with FH as above average (>4, from a scale of 1 to 7). Although self-perceived familiarity with FH was not significantly different among most countries (except lower in Japan and China) and the United Kingdom, awareness of FH guidelines was significantly lower in Asia-Pacific compared with the United Kingdom (35% vs 61%, p<0.001). Similarly, the awareness of lipid specialists for referral or medical advice was significantly lower in Asia-Pacific compared with the United Kingdom (35% vs 50%, p=0.003); only Australian and Taiwanese PCPs were comparably aware. Regarding the knowledge of FH, PCPs from the United Kingdom were significantly better at selecting the correct FH description (89% vs 72%, p=0.001) compared with the Asia-Pacific PCPs.

Table 2 details the comparison of PCP's responses to questions about FH awareness, knowledge, practices and preferences with the United Kingdom as the reference group. In spite of the lower self-perceived familiarity with FH, Japanese and Chinese physicians were significantly better at identifying the correct FH lipid profile, compared with the United Kingdom. The response to questions concerning the prevalence, inheritance and CVD risk of FH were suboptimal in all countries/regions, and particularly in China and Vietnam. Half of the PCPs correctly identified that genetic testing was not required to accurately diagnose FH. The majority of PCPs selected statins as the best pharmacotherapy to best treat hypercholesterolaemia, with a significantly lower proportion of PCPs selecting this from Japan and Vietnam, compared with the United Kingdom. Half of the PCPs selected the combination of statin and ezetimibe to treat severe hypercholesterolemia, with a significantly higher proportion of PCPs selecting this from Australia, South Korea and China, compared with the United Kingdom.

Concerning practices relating to FH, PCPs from the Asia-Pacific region and the United Kingdom were equally likely to screen patients with premature CAD for their family history of CVD. Of PCPs who had FH patients under their care, 66% from Asia-Pacific and 73% the United Kingdom responded that they would perform routine screening of their family members and there was no significant difference. However, Japanese PCPs caring for FH patients were the lowest who would undertake family

screening among the countries/regions. The most prevalent age for screening young people in a kindred with FH was selected at 13-18 years. Although awareness of lipid specialists were suboptimal, in PCPs that were aware of lipid specialists, only 56% had referred FH patients to a lipid specialist in the Asia-Pacific region, compared with 72% in the United Kingdom which was significantly higher (p=0.028); Japan, Philippines, Vietnam and Malaysia were particularly low.

The majority of PCPs from the United Kingdom (82%) selected themselves as the most effective health care provider for the early detection of FH. However, the response was highly disparate in the Asia-Pacific region, with only 8% of responses from China and 23% from Vietnam identifying PCPs as the preferred health care provider for the early detection of FH. By contrast, 92% of from Malaysia and 80% from Australia, selected PCPs (Table 1). Overall, cardiologists (38%), lipid specialists (36%) and endocrinologists (10%) were also selected by the PCPs from the Asia-Pacific. However, PCPs did not consider that there was a significant role for paediatricians, obstetricians/gynaecologists and/or nurses with cardiac training in the care of FH. The majority of PCPs selected an interpretive laboratory comment on lipid test report results as being useful in detecting FH.

DISCUSSION

Recent knowledge of the population frequency of FH suggests that it can be viewed as a public health problem. Strategies for improving early diagnosis and care of FH in the community requires adequate knowledge and appropriate practices concerning this condition. This study is the first survey to demonstrate significant gaps in knowledge and awareness of FH across several countries/regions in the Asia-Pacific and to identify important areas of deficit.

In the present study, the lack of awareness of guidelines and lipid specialists can be related to the lack of country-specific guidelines[16] on FH and the lack of physicians specifically trained and practicing as lipid experts in the region. Although the UK performed significantly better on these questions compared with the countries/regions in the Asia-Pacific, the results were still suboptimal. 39% were unaware of FH guidelines despite the fact that the NICE guidelines for identifying FH were released 7-8 years ago, and 50% were not aware of a lipid specialist in spite of the efforts from Heart UK in mapping specialist lipid clinics and establishing an FH

Intelligence Network. Lack of awareness of clinical services for lipid disorders may be because specialist services do not exist in their geographical area, particularly for PCPs practising in suburban and rural regions, which constituted 43% of the PCPs surveyed.

The PCPs were generally able to correctly define FH. However, knowledge of FH prevalence, heritability and risk of CVD were suboptimal. Three quarters of PCPs in the present study were not aware of the theoretical prevalence of FH of 1:500 (with 42% selecting 'don't know') and 91% were not aware of the >20-fold risk of CVD in untreated FH[17] (with 30% selecting 'don't know'). However, as demonstrated by recent studies, heterozygous FH may be more common than 1:500[2-6] and given the sparse prevalence data from the region and the exceptionally high prevalence reported in the Hokuriku district of Japan[18], the true prevalence of FH in the region is undefined. Additionally, CVD risk could be ~10-fold[19] and the relative risk of CVD with FH also varies significantly by age. Taking this into account, 45% of respondents identified the prevalence as between 1:100-1:1000 and 60% selected CVD risk to be 5-20 times greater. Although still suboptimal, this at least indicates an understanding that the risk of CVD is high among patients with FH.

Knowledge and familiarity with lipid-lowering treatment was reassuring; most PCPs identified statins to best treat hypercholesterolaemia. A lower proportion of physicians from Japan and Vietnam selected statins, which may relate to the availability of alternative medication (eg. probucol) and the lack of access to statins in some regions. Owing to the severity of hypercholesterolaemia, most FH patients will require additional therapy to reach treatment goals[1]. PCPs from China, South Korea and Australia were particularly good at selecting combination statin and ezetimibe therapy for treating severe hypercholestolaemia. By contrast, selection of combination statin and ezetimibe therapy in Vietnam was low and this may relate to the lack of general access to pharmacotherapies.

PCPs are critical in achieving long-term treatment adherence and have a key role in recognising family history of premature CAD. An accurate family history is integral to both CVD risk assessment and the diagnosis of FH. Encouragingly, 90% of PCPs would take a detailed family history in patients with premature CAD. However, there were gaps in cascade screening of close relatives, especially in Japan. Although the

European guidelines suggest screening of children in an FH kindred from the age of 5 years[20] and the NICE guidelines recommend screening children between 2-10 years, PCPs in the Asia-Pacific region considered that testing between 13-18 years of age was a more appropriate practice. Studies on cholesterol screening in US paediatricians raised concerns regarding conflicting guidelines on lipid screening and treatment practices[21] and half of the paediatricians were opposed to the use of lipid-lowering therapies in children[21 22].

Differences in the choice of healthcare professional perceived as best suited for managing FH and family screening among the countries/regions may reflect different healthcare systems. In particular, 83% of Chinese PCPs considered that lipid specialists were better suited to manage FH. There was the view that cardiologists are well positioned to identify index cases with FH presenting with coronary events[23 24]. Similarly, endocrinologists were considered well placed to identify FH in a secondary prevention setting. Overall, respondents in the present study considered that PCPs were best situated to identify FH in the primary prevention setting. Few considered that there was a significant role for nurses. This differs from the Netherlands[25] where screening programs have been conducted by nursing and/or allied health staff. 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. Further exploration of health services and systems are warranted to optimise country-specific clinical service models and integration of care[1].

The majority of PCPs in the present study thought that interpretative commenting attached to the reports on lipid profiles in people at high-risk of FH would be useful. This mode of alerting could play a role in the detection and management of FH[26]. Electronic screening tools to retrospectively identfiy FH in general practices could also be useful; some preliminary work from the United Kingdom and Australia has demonstrated the potential to increase identification of FH via this method[27-29]. Other methods such as screening via the laboratory[30 31] and improving communication between the requesting physican and the chemical pathologist[32] may also be useful. Implementing these in service mode will require an integrated collaborative approach with local laboratories, pathologists and treating physcians.

Increased lipoprotein(a), smoking, hypertension and diabetes are all known to compound CVD risk and are predictors of CAD in FH[33-40]. A limitation of the present survey was that CVD risk factors were not explored, particularly with the increasing prevalence of risk factors in Asia[41]. The use of genetic testing was also not explored. Other limitation of the study may be the self-selected group that responded to the questionnaire and may reflect those with more interest and knowledge in lipid disorders; the present study may not have captured the widest gaps in knowledge and awareness of FH. Since the survey was conducted anonymously, there was no recorded information on responders and non-responders. The analyses also assumed that the United Kingdom PCPs were the gold standard responders and since the United Kingdom was the only country to administer the questionnaire via an online survey and mailing list, this may have biased responses. The generalisability of our results is constrained by the characteristics of the sample population. Extended enquires before and after education are required in the field. Given that primary care also involves other health professionals, such as practice nurses and allied health professionals, future studies should also be directed at these groups.

Similar surveys have been undertaken in PCPs[12] and pharmacists[42] in Western Australia, cardiologists in the US[24] and physicians in India[43], as well as a pilot study among physicians in Japan, South Korea, Taiwan[7]. Knowledge shortfalls were comparable, with underestimations of prevalence, hereditability and CVD risk. A recent study by *Schofield* et al[44] assessed FH knowledge among a diverse group of health care professionals (including nurses and pharmacists in the United Kingdom and demonstrated knowledge gaps in FH prevalence, diagnostic criteria and treatment options. In a smaller cohort (n=35) of health care professionals that completed a second survey following an FH education session, all aspects of FH knowledge was improved. *Bell* et al[45] have also shown that with direct education, PCPs are able to accurately assess FH. This emphasises the important of investing in FH education programs[46]. A global initiative, the European Atherosclerosis Society FH Studies Collaboration was launched with aims to disseminate information to empower the medical and lay community to seek changes to improve the care of patients and families with FH[47]. Education programs in medical schools[48] and accredited courses with continuing professional development points could be useful.

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.

Screening programs in the region have been communicated by Singapore[49] and Hong Kong[50]. Owing to high population densities in the region, family cascade screening after the detection of an index case with FH could be particularly efficient and cost-effective. However, specific diagnostic criteria and guidelines in the region are only available from Australia[51], Japan[52] and South Korea[53]. The Australasian model of care is a comprehensive clinical guideline encompassing elements of index case detection, diagnosis and assessment, management, cascade screening, genetic testing and the organisation of clinical services[51]. The Japanese criteria are based on the detection of tendon xanthomata[52], which may only be present in ~30% of FH patients and particularly uncommon in the young[54], and hence may have low sensitivity in screening and detecting FH. A study from South Korea demonstrated the lack of detection power with all conventional clinical criteria and suggested an LDL-C cut-off of 225mg/dL (~5.8mmol/L)[53]. However, the LDL-C cut-off was derived from a biased sample of patients with existing hypercholesterolemia. The lack of country-specific criteria may contribute to the lack of active screening programs employed in the region and the cost of genetic testing in the community beyond research studies is not justified. FH research in the region is highly warranted; the mutation spectrum of FH is different from the European spectrum[55] and the mean cholesterol concentrations in most Asian countries are lower compared with Western countries[16]. 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[17 56].

The integrated international guidance on FH[1], endorsed by the Asian-Pacific Society of Atherosclerosis and Vascular Disease[57], provides a foundation for developing country-specific guidelines, services and models of care. The principles are similar, but require the development of country-specific recommendations to screen,

diagnose and treat FH, as well as strategies for long-term adherence and goal attainment[58]. Country-specific challenges in developing screening programs may relate to their healthcare systems, as well as diverse cultures, political systems and economies[59 60] in the region. Challenges in treatment and management include the tolerability of statins, its availability and affordability[61], and its acceptability against the popularity of complementary and alternative medicines[62 63]. The FH "Ten Countries Study" group is the first collaborative effort in the region focusing specifically on FH and should hopefully see the extension of the series of studies, including the present study, into the translation and transference of the research findings to country-specific models of cares[13].

CONCLUSION

The present study identified substantial deficits in FH knowledge and awareness among physicians in the Asia-Pacific region, in particular, awareness of guidelines and knowledge of diagnostic features of FH. Knowledge of FH hereditability, prevalence and CVD risk were also suboptimal. Major treatment gaps were identified in Vietnam and gaps in family screening were noted in Japan. However, through extensive FH education, awareness programs and implementation of country-specific guidelines, these gaps can be addressed to accelerate the pace of FH diagnosis and treatment. Similar surveys are required in specialists practicing coronary prevention in the region. A potentially effective method of standardising care across countries is participation in an international registry[64].

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Competing interests

All authors have completed the Unified Competing Interest form. TM reports grants from JSPS during the conduct of the study; grants from Denka-Seiken, Shino-test, MSD and Otsuka outside the submitted work; and honoraria from Sanofi, Astellas-Amgen, Astra Zeneka, Otsuka, Takeda, Kowa, Denka-Seiken, Sekisui-Medical, Kyowa Medex and Wako. HS reports research grants from Alexion, Amgen, MSD and Pfizer; and personal fees and education grants from Aegerion, Amgen, Janssen Cilag Ltd, MSD, Pfizer,Novo Nordisk and Sanofi. SY reports grants and personal fees from Kowa, Otsuka, Shionogi, Bayer Yakuhin, MSD, Takeda, Sanwa Kagaku Kenkyusho, Astellas, Daiichi-Sankyo, Astra Zeneca and Kaken; grants from Nippon Boehringer Ingelheim, Kyowa Medex, Mochida, Hayashibara, Teijin, Kissei and National Institute of Biomedical Innovation; and personal fees from Medical Review Co., Skylight Biotech, Pfizer, Bristol-Meyers, Astellas-Amgen, Sanofi, Agerion and Toa Eiyou, outside the submitted work. In addition, SY has two pending patents, Fujirebio and Kyowa Medex. BT reports grants and personal fees from Amgen; grants from AstraZeneca, Merk Sharp & Dohme, Novartis, Pfizer and Roche; personal fees from Merck Serono and Sanofi, outside the submitted work. GFW reports grants from Sanofi /Regeneron during the conduct of the study; grants and personal fees from Sanofi /Regeneron and Amgen; personal fees from Gemphire and

Kowa, outside the submitted work. JP, THT, NTK, ASR, JEP, LGS, JL, XW, MH, HMN and SK have nothing to disclose.

Contributorship statement

JP designed data collection tools, implemented the study for the all countries, monitored data collection, cleaned and analysed the data, and drafted and revised the paper. MH and BT implemented the study in Hong Kong and revised the draft paper. JL and XW implemented the study in China and revised the draft paper. TM and SY implemented the study in Japan and revised the draft paper. HMN and ASR implemented the study in Malaysia and revised the draft paper. JEP implemented the study in South Korea and revised the draft paper. THT and NTK implemented the study in Vietnam and revised the draft paper. HS and SK implemented the study in the United Kingdom and revised the draft paper. LGS implemented the study in the Philippines and revised the draft paper. TS implemented the study in Taiwan and revised the draft paper. GFW initiated the collaborative project, designed data collection tools, implemented the study for the all countries, advised the statistical analysis plan and revised the paper.

Transparency declaration

JP affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Date sharing statement

No additional data available. Extra details on data presented in the current study is available by emailing jing.pang@uwa.edu.au.

Table 1: Summary of PCP's demographics and responses to questions (%) about awareness, knowledge, practices and preferences regarding FH in "Ten Countries".

Country/Region	Australia	Japan	Malaysia	South Korea	Philippines	Hong Kong	China	Vietnam	Taiwan	United Kingdom[15]
Number of PCPs	**151**	**197**	**219**	**97**	**62**	**59**	**118**	**137**	**38**	**100**
DEMOGRAPHICS										
Male	62%	84%	24%	81%	37%	53%	42%	46%	74%	42%
Urban/Metropolitan	52%	49%	63%	82%	63%	100%	82%	40%	100%	47%
Suburban/Outer metropolitan	33%	30%	0%	14%	15%	0%	18%	27%	0%	44%
Rural	16%	21%	37%	4%	23%	0%	0%	33%	0%	9%
AWARENESS										
Familiarity of FH rated as above average	32%	23%	38%	28%	34%	50%	23%	49%	47%	39%
Awareness about FH guidelines	36%	47%	35%	34%	N/A	43%	8%	28%	53%	61%
Awareness about lipid specialists	51%	33%	34%	30%	31%	40%	12%	39%	57%	50%
KNOWLEDGE										
Correctly described FH	72%	77%	86%	51%	73%	62%	75%	65%	60%	89%
Correctly identified lipid profile	59%	85%	65%	57%	48%	51%	85%	45%	61%	74%
Correctly identified prevalence of FH in the community	26%	41%	24%	19%	16%	11%	17%	14%	30%	30%
Correctly identified the transmission rate of FH to first degree relatives	44%	40%	49%	42%	37%	49%	36%	26%	61%	51%
Correctly identified the CVD risk in untreated FH patients	14%	13%	9%	8%	10%	7%	4%	2%	5%	14%
Correctly identified that genetic testing was not required to accurately diagnose FH	50%	52%	47%	64%	68%	38%	38%	58%	24%	52%
Selected statins to best treat hypercholesterolemia	89%	85%	96%	90%	95%	93%	95%	75%	95%	94%
Selected a combination of statin and ezetimibe to treat severe hypercholesterolemia	64%	48%	56%	70%	48%	49%	77%	31%	63%	50%
PRACTICE										
Screened patients with premature CAD for family history	93%	83%	95%	89%	92%	95%	94%	85%	95%	90%
Performed routine family screening of patients with FH (if there were FH patients under their care)	86%	30%	82%	50%	53%	90%	47%	83%	77%	73%
The most prevalent age for screening young people in a kindred with FH was 13-18 years, which was selected by	52%	18%	52%	54%	52%	48%	16%	33%	20%	45%
Have referred FH patients to a lipid specialists (if aware of lipid specialist)	66%	26%	52%	57%	32%	86%	86%	49%	100%	72%
PREFERENCE										
Selected PCPs as the most effective health care provider for the early detection of FH	80%	45%	92%	71%	58%	76%	8%	23%	50%	82%
Selected interpretive commenting on lipid profiles to highlight patients at risk of FH	89%	57%	92%	84%	92%	85%	86%	72%	89%	88%

Table 2: Comparison of PCP's responses to questions about FH awareness, knowledge, practices and preferences with the United Kingdom as the reference group using logistic regression analyses; odds ratio (95% confidence interval) shown.

Country/Region	Australia	Japan	Malaysia	South Korea	Philippines	Hong Kong	China	Vietnam	Taiwan
AWARENESS									
Familiarity of FH rated as above average	0.73 (0.43-1.24)	0.47 (0.28-0.79)*	0.95 (0.58-1.55)	0.61 (0.33-1.11)	0.80 (0.41-1.55)	1.56 (0.81-3.01)	0.46 (0.25-0.83)*	1.52 (0.90-2.57)	1.41 (0.66-2.99)
Awareness about FH guidelines	0.34 (0.21-0.61)**	0.58 (0.36-0.95)*	0.35 (0.22-0.58)**	0.34 (0.19-0.61)**	N/A	0.49 (0.26-0.95)*	0.05 (0.02-0.12)**	0.25 (0.14-0.43)**	0.72 (0.34-1.53)
Awareness about lipid specialists	1.03 (0.62-1.71)	0.5 (0.30-0.82)*	0.51 (0.31-0.83)*	0.43 (0.24-0.78)*	0.44 (0.23-0.86)*	0.68 (0.35-1.31)	0.14 (0.07-0.27)**	0.64 (0.37-1.11)	1.33 (0.61-2.90)
KNOWLEDGE									
Correctly described FH	0.33 (0.16-0.68)*	0.42 (0.21-0.86)*	0.78 (0.37-1.62)	0.13 (0.06-0.28)**	0.34 (0.15-0.78)*	0.21 (0.09-0.48)**	0.38 (0.18-0.82)*	0.24 (0.12-0.50)**	0.19 (0.07-0.50)*
Correctly identified lipid profile	0.52 (0.30-0.90)*	2.06 (1.12-3.77)*	0.65 (0.38-1.10)	0.47 (0.26-0.85)*	0.33 (0.17-0.65)*	0.37 (0.18-0.65)*	2.07 (1.05-4.10)*	0.29 (0.16-0.51)**	0.55 (0.25-1.20)
Correctly identified prevalence of FH in the community	0.80 (0.46-1.41)	1.60 (0.96-2.69)	0.73 (0.43-1.25)	0.54 (0.27-1.06)	0.44 (0.20-0.99)	0.28 (0.11-0.71)*	0.49 (0.25-0.93)*	0.38 (0.20-0.73)*	0.97 (0.43-2.22)
Correctly identified the transmission rate of FH to first degree relatives	0.74 (0.44-1.23)	0.63 (0.39-1.03)	0.91 (0.56-1.48)	0.70 (0.38-1.27)	0.57 (0.30-1.08)	0.92 (0.46-1.84)	0.54 (0.31-0.93)*	0.34 (0.19-0.59)**	1.52 (0.68-3.46)
Correctly identified the CVD risk in untreated FH patients	0.97 (0.46-2.02)	0.90 (0.44-1.83)	0.59 (0.28-1.22)	0.56 (0.22-1.40)	0.66 (0.24-1.81)	0.46 (0.14-1.48)	0.28 (0.10-0.81)*	0.15 (0.04-0.52)*	0.34 (0.07-1.58)
Correctly identified that genetic testing was not required to accurately diagnose FH	0.91 (0.55-1.51)	1.00 (0.61-1.62)	0.83 (0.51-1.33)	1.63 (0.92-2.90)	1.94 (1.00-3.76)	0.56 (0.29-1.09)	0.56 (0.33-0.97)*	1.28 (0.76-2.17)	0.30 (0.13-0.96)*
Selected statins to best treat hypercholesterolemia	0.50 (0.19-1.32)	0.37 (0.15-0.92)*	1.68 (0.57-4.99)	0.56 (0.19-1.59)	1.26 (0.30-5.21)	0.88 (0.24-3.25)	1.19 (0.37-3.82)	0.19 (0.08-0.48)*	0.74 (0.18-3.14)
Selected a combination of statin and ezetimibe to treat severe hypercholesterolemia	1.75 (1.04-2.92)*	0.91 (0.56-1.48)	1.26 (0.78-2.02)	2.34 (1.31-4.21)*	0.94 (0.50-1.77)	0.97 (0.51-1.84)	3.37 (1.88-6.03)**	0.46 (0.27-0.78)*	1.71 (0.80-3.69)
PRACTICE									
Screened patients with premature CAD for family history	1.57 (0.63-3.91)	0.53 (0.25-1.23)	2.10 (0.86-5.12)	0.87 (0.35-2.15)	1.27 (0.41-3.90)	2.07 (0.55-7.86	1.76 (0.65-4.81)	0.61 (0.28-1.37)	2.00 (0.42-9.58)
Performed routine family screening of patients with FH (if there were FH patients under their care)	2.25 (0.81-6.22)	0.16 (0.06-0.40)**	1.75 (0.65-4.70)	0.38 (0.14-1.04)	0.43 (0.17-1.06)	3.38 (0.93-12.21)	0.34 (0.10-1.10)	1.88 (0.34-10.27)	1.23 (0.39-3.86)
Selected 13-18 years as most appropriate for screening young people in a kindred with FH	1.32 (0.79-2.21)	0.27 (0.16-0.47)**	1.30 (0.81-2.10)	1.42 (0.81-2.51)	1.28 (0.68-2.42)	1.12 (0.58-2.15)	0.23 (0.12-0.43)**	0.59 (0.34-1.02)	0.30 (0.12-0.75)*
Have referred FH patients to a lipid specialists (if aware of lipid specialist)	0.75 (0.34-1.64)	0.14 (0.06-0.32)**	0.42 (0.20-0.91)*	0.52 (0.20-1.37)	0.18 (0.06-0.57)*	2.33 (0.59-9.18)	2.33 (0.46-11.78)	0.37 (0.15-0.88)*	1
PREFERENCE									
Selected PCPs as the most effective health care provider for the early detection of FH	0.89 (0.46-1.69)	0.18 (0.10-0.32)**	2.61 (1.28-5.31)*	0.54 (0.28-1.06)	0.30 (0.15-0.62)*	0.71 (0.32-1.55)	0.02 (0.01-0.05)**	0.07 (0.04-0.13)**	0.22 (0.10-0.50)**
Selected interpretive commenting on lipid profiles to highlight patients at risk of FH	1.15 (0.52-2.55)	0.18 (0.09-0.35)*	1.52 (0.70-3.30)**	0.69 (0.31-1.55)	1.55 (0.52-4.65)	0.76 (0.30-1.92)	0.81 (0.37-1.79)	0.36 (0.17-0.72)*	1.16 (0.35-3.84)

*p<0.05, **p<0.001, significantly less than the United Kingdom, significantly more than the United Kingdom.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

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	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	5-6
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6 & 15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
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	17
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
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	4 & 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
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	13

*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.