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An Epidemiological Survey of Venous Disease Among General Practitioner Attendees in Different Geographical Regions on the Globe: The Final Results of the Vein Consult Program

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Abstract

This study measured the prevalence of chronic venous disease (CVD, C1-C6), chronic venous insufficiency (C3-C6) in 23 countries. The possible influence of risk factors was assessed. Patient recruitment was carried out by general practitioners. Patient characteristics, prevalence of risk factors, and C-classification were recorded. We assessed differences in prevalence and risk factors between Asia (A), Eastern Europe (EE), Latin America (LA), and Western Europe (WE). A total of 99 359 patients were included. The prevalence of CVD (51.9% A, 70.18% EE, 68.11% LA, and 61.65% WE) was significantly ($P < .001$) lower in A. Risk factors such as age, obesity, smoking, having regular exercise, use of birth control pills, prolonged standing and sitting, and having a positive family history differ significantly between regions. After model-based probabilities corrected for risk factors, significant differences in the probability of having CVD were only found in the older age-group (>65 years). The lowest prevalence was noted in A. Chronic venous disease is very common and the prevalence varies between different geographical areas. After correcting for risk factors, these differences diminished.

Keywords

venous disease, epidemiological study, Vein Consult Program

Introduction

Chronic venous disease (CVD) is one of the commonest disorders in Northern and Western Europe (WE).[1-4] Estimates of its prevalence vary depending on the population, ethnicity, selection criteria, disease definition, and imaging techniques used. The age-stratified prevalence of truncal varicose veins (including incompetence of the great, small anterior accessory saphenous vein, or incompetent perforating veins) measured in the Edinburgh Vein study was 11.5% in the 18 to 24 age-group, increasing to 55.7% in the 55 to 64 age-group.[2,5]

In order to report the extent of the venous disease (VeD) more accurately, the clinical, etiological, anatomical, and pathological classification (CEAP classification) was introduced in 1994[6] and updated in 2004.[7] This classification is based on clinical manifestations (C), etiological factors (E), anatomic distribution of disease (A), and underlying pathophysiological findings (P). In this survey, we only use the C-classification.

In a population-based study (Bonn Vein Study[8,9]), classification levels (CEAP-classification) were 59.0% C1, 14.3% C2, 13.5%, C3, 2.9% C4, and 0.7% C5 to C6. A recent epidemiological study in Belgium and Luxembourg revealed a prevalence of CVD (C1-C6) of 61.3% and chronic venous insufficiency (CVI) of 25.9%.[10]

The most common symptoms of CVD are, respectively, in declining order, having "heavy legs," sensation of pain, sensation of swelling and burning, having night cramps, itching, and having the sensation of "pins and needles." The presence and the severity of these symptoms are clearly worsened by age and female gender.[11]

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Other important risk factors include, respectively, "having a positive family history of CVD," having a higher body mass index (BMI), not "having regular exercise," number of pregnancies, number of hours standing a day, number of hours sitting a day, the use of birth control pills, and smoking (past or current).[10]

Chronic venous disease is defined as any morphological and functional abnormalities of the venous system.[12] Practically, this includes patients with a C-score from C1 to C6. The term CVI implies a functional abnormality of the venous system and is usually reserved for more severe diseases including edema, skin changes, or venous ulcers (C3-C6).[1,12,13]

The prevalence of CVD may vary from country to country or from continent to continent. It has always been believed that CVD has the highest prevalence in Western European countries. Risk factors may, however, differ from region to region.

This study is part of the Vein Consult Program (VCP). The VCP is the greatest global effort to raise awareness about CVD among patients, health-care professionals, and health authorities and was initiated by the International Union of Phlebology with a grant from Servier. It aims to assess the prevalence of CVD in varying geographical areas. The VCP has been carried out in many countries.[10,11,14-19] The advantage of the VCP is that the same protocol has been used in each participating country, which makes it possible to compare the results.

The aim of this study is to measure the prevalence of VeD, more specifically CVD (C1-C6) and CVI (C3-C6) in 23 different countries around the world and to look for regional differences. The possible influence of risk factors is also assessed. This article presents the final results of the VCP and contains the largest sample size of all previous published epidemiological studies on VD.

Materials and Methods

Patients were recruited by selected general practitioners (GPs) in different countries. General practitioners were selected in compliance with national regulations, usually at random from a national registration list. Each of them included 10 to 20 consecutive patients who attended the practice for various reasons. Patients under the age of 18 years or attending for emergency visits were excluded. Informed consent was obtained from each participant. Patients needed to be enrolled within a short period of time. Before patient intake, the GPs received a training in recognizing VeD. This means the representative of Servier explained in detail the protocol to the GP, how to recognize the signs and symptoms of VeD and how to complete the questionnaire. The GPs received an illustrated guide on the C-classification to ensure they adequately reported the C-class of each patient in the case report form. For each participating patient, the GP completed a report assessing the patient's history, listing any CVD risk factors, screening for CVD symptoms and performing a routine leg examination. The GP scored the patients according to the C-classification by visual examination. No ultrasound was carried out.[20,21]

This VCP protocol has been described in detail.[10,11,14-19] The survey was approved by the ethics committee in all of the participating countries (n = 23).

In this article, all data of the VCP were used, with an exception of some data from 1 country. It was noted that they have reported a surprisingly high number of patients with healed or active ulcers (7% and 10%, respectively). Since these abnormal data were exclusively found in data from patients recorded in 1 particular year, we expected this to be due to an error in the completion of the database. Therefore, these data were excluded. As a result of this, the total number of included patients decreased (from 120 338 to 99 359).

Data analysis was performed. We calculated the prevalence of CVD and CVI in the different regions. We looked for possible significant differences. Correction for age gender was made by separately reporting results for each gender and different age groups. The influence of the risk factors on the prevalence of VD was assessed. Estimates of prevalence of CVD and CVI and significance in difference between the regions were calculated as odds ratios (OR). These ORs were adjusted for risk factors.

Statistical Analyses

Analyses were performed in SAS 9.4 (SAS Institute, Cary, North Carolina). Differences in risk factors between regions were compared using χ^2 tests for the categorical ones (gender, obesity [BMI >30], positive family history of VD, and smoking) and using Kruskal-Wallis tests for the numerical ones (age, number of births, hours sitting, hours standing).

Probabilities for VD were estimated using a mixed logistic regression (PROC GLIMMIX procedure enables you to specify a generalized linear mixed model and to perform confirmatory inference in such models) with region, gender, and age (years) as fixed factors and GP and country as random factors. This model allows us to test for the interaction between region, age, and gender. To investigate the differences in terms of the proportion of CVD and CVI between regions, mixed logistic regression models were applied separately for each combination of gender and age category with GP and country as random factors and region as a fixed factor.

Additionally, to compare the probabilities of CVD and CVI between regions after adjusting for risk factors, for example, obesity, positive family history, regular exercise, smoking, hours sitting, and hours standing were included as fixed factors. For all tests, a 2-sided $P < .05$ was considered significant.

Results

The VCP was conducted between October 2009 and September 2013 in 23 different countries. A total of 5844 GPs participated in this survey. In all, 99 359 patients were included. The average age was 51.8 years and the female predominance 70.7%. We defined 4 different regions: Asia (A), Eastern Europe (EE), Latin America (LA), and WE (Table 1).

Table 1. Number of Included Patients Related to Region and Country.

Region	Country	Number of Included Patients	Total for Overall Region
Asia			
	Georgia	3597	n = 12 288 (12.37%)
	Indonesia	1436	
	Pakistan	3163	
	Singapore	329	
	Thailand	901	
	United Arab Emirates	494	
	Vietnam	2368	
Eastern Europe			
	Armenia	1551	n = 30 110 (30.3%)
	Bulgaria	2180	
	Hungary	5383	
	Romania	4902	
	Russia	5579	
	Slovenia	487	
	Ukraine	3863	
	Serbia	2975	
	Slovakia	3190	
Latin America			
	Brazil	868	n = 10 020 (10.08%)
	Colombia	4569	
	Mexico	4583	
Western Europe			
	Belgium	5383	n = 46 941 (47.24%)
	France	23 980	
	Luxembourg	112	
	Spain	17 466	

In total, 69.94% of the included patients were diagnosed as having CVeD (C1-C6). Chronic venous insufficiency (C3-C6) was noted in 32.3%; 9.1% of all patients did have an active or a healed ulcer. This prevalence, however, differs between the different regions with the lowest score (for CVD, CVI) as measured in A (Tables 2 and 3).

Patients in WE (mean 53.2 years) and EE (mean 54.4 years) were significantly older than those from LA (mean 44.4 years) and A (mean 46.4 years; Kruskal-Wallis; $P < .001$). Asian patients had a significantly lower positive family history, were less obese, less smoking but had a higher number of births compared with other regions. These factors may contribute to a lower prevalence of VD in A. However, the number of births was highest in A compared with the other regions (Table 4).

Since age and gender have an important influence on the prevalence of VD, estimated probabilities were corrected for age (using age groups) and reported separately for males and females (Table 5).

The differences in VD between regions depend on gender ($P < .001$; for interaction between region and gender). For this reason, the effect of region on the proportions of CVD and CVI were tested separately for each combination of age-group (age as a categorical variable) and gender (Table 5).

Several risk factors were assessed. Unfortunately, some databases were incomplete. For example, the variable "number of births" contains a large amount of missing values (37.1%). For this reason, only the risk factors "smoking," "family history of CVD," "regular exercise," "number of hours spent standing," "number of hours spent sitting," "use of birth control pills (female patients)," and "obesity (BMI >30)" were included in the model.

We could not find any significant difference between regions in terms of the predicted probability of having CVD in male patients for all age groups. However, for female patients, we found a significant difference in the predicted prevalence for age-group older than 51 years, with the lowest probabilities in Asian patients (age-group: 51-65 and >65 years). However, that difference was only significant compared with LA and EE, not compared to WE.

Regarding the more advanced patient group (CVI), we calculated separately the predicted probability of having CVI for each gender and age-group (Table 5). In the younger age groups (<51 years), no significant differences could be found between male and female patients. In male patients, we only found a significant difference in the estimated prevalence in the age-group (51-64 years), with a significant lower prevalence in A compared with EE ($P = .018$) and LA ($P = .023$). However, no significant differences could be found comparing A and WE ($P = .696$). In female patients, we found a significant difference in the oldest age-group (>65 years) comparing A and EE ($P = .0184$) and LA ($P = .015$), with the lowest prevalence in A. No significant difference could be found in the predicted prevalence having CVI between A and E in this age-group.

Most measured risk factors had a significant influence on the prevalence of CVD, but this also depended on the age groups (Table 6). So did the "use of birth control pills" influence the prevalence of CVD in patients younger than 51 years? This influence was not significant anymore in older female patients. Smoking only influenced young patients (<35 years). In the younger age-group (18-34 years), all risk factors (n = 8) did have a significant influence on the predicted prevalence of CVD. However, some risk factors having a significant influence lose their influence in older age groups. In the age-group of 51 to 65 years, no significant influences on the predicted probability of CVD could be found for risk factors "smoking," "number of hours sitting a day," and "the intake of birth control tablets."

Mixed logistic regression tests were used to adjust the model-based probabilities of having CVD for each gender and age-group. Estimates of prevalence of CVD and significance in difference between the regions were calculated as ORs (Table 7). These differences were adjusted for all included risk factors. Most significant differences disappeared, with an exception for female patients older than 65 years (Table 7). Asian female patients had a significant lower predicted prevalence of having CVD compared with EE and LA. In all other age-group, the differences were not significant anymore.

Table 2. Clinical Classification by Region.

CEAP	Asia	Eastern Europe	Latin America	Western Europe	Total
0	n = 5907 (48.07%)	n = 8980 (31.89%)	n = 3195 (31.89%)	n = 18 000 (38.35%)	n = 36 082
1	n = 2257 (18.37%)	n = 5712 (18.97%)	n = 2238 (25.16%)	n = 10 057 (21.42%)	n = 20 264
2	n = 1686 (13.72%)	n = 6414 (21.30%)	n = 1920 (19.16%)	n = 7207 (15.35%)	n = 17 227
3	n = 1665 (13.55%)	n = 5276 (17.52%)	n = 1340 (13.37%)	n = 7437 (15.84%)	n = 15 718
4	n = 616 (5.01%)	n = 2864 (9.51%)	n = 930 (9.28%)	n = 3457 (7.36%)	n = 7867
5	n = 73 (0.59%)	n = 628 (2.09%)	n = 250 (2.50%)	n = 578 (1.23%)	n = 1529
6	n = 84 (0.68%)	n = 236 (0.78%)	n = 147 (1.47%)	n = 205 (0.44%)	n = 672
Total	n = 12 288	n = 30 110	n = 10 020	n = 46 941	n = 99 359

Abbreviation: CEAP, the Clinical, Etiological, Anatomical and Pathological Classification.

Table 3. Prevalence of Chronic Venous Disease (CVD) and Chronic Venous Insufficiency (CVI) in the Different Regions.

Region	CVD (C1-C6)	CVI (C3-C6)
Asia	51.93%	19.84%
Eastern Europe	70.18%	29.90%
Latin America	68.11%	26.62%
Western Europe	61.65%	24.88%
Overall	63.69%	25.95%

Discussion

Chronic venous disease (C1-C6) is very common worldwide. The highest prevalence was in EE (70.18%) and the lowest in A (51.93%). This result does, in contrast to previous VCP publications, not include patients with level C0s (patients with symptoms of CVD but without clinical signs). This category may be open to challenge since some of the symptoms in C0s patients may be due to non-CVD disorders.

This survey measured the prevalence of CVD and CVI in a population visiting a GP. This does not exactly represent the average population in different countries. Also, due to the fact that patients younger than 18 years were excluded, the age of patients included in this survey was older than the average age in the different countries. In addition, more female patients were included than males. This leads to an overestimation of the measured prevalence of CVD (and CVI). Nevertheless, the measured prevalence is impressive and not very different compared with other surveys using CEAP score.[8,15,16,22] The separate calculation of the predicted probability of having VD for each gender and different age (correcting for age and gender) could partially correct the overestimation.

In this survey, the diagnosis of VD was made by the GP. Using an illustrated guide, the patients were recorded according to the C-classification. However, no duplex ultrasound was performed. So the scoring may not always be correct: Edema (C3) might also have another underlying pathology than VD. Skin changes can be due to VD but also be primary dermatologic. As also not every ulcer is related to venous incompetence. The interobserver reproducibility, according to literature, is rather poor (47%).[23] There was no specific quality assurance program. This might be a cause of some misdiagnosis of the VD or misclassification according to the CEAP score.

We wanted to measure the difference in prevalence of VD between the different regions. We distinguished 4 different regions: WE, A, LA, and EE. This selection may be open to dispute. We have data from 23 countries, which is not representative of the global population. With the exception of A, there is no clear difference in ethnicity between those regions. Participants from LA may have a mixed ethnicity. Even between countries from a single region, differences in prevalence can be noted. So we found that patients from Spain[19] have a lower prevalence of CVD compared with Belgian patients[10,11] (48.5% vs 61.3%). The mean age in the Spanish and Belgian population was, respectively, 53.7 and 53.4 years. Unfortunately, the database did not include data of patients from Africa or North America. Information from Africa would have been particularly interesting as we could have looked for the ethnic influence on the prevalence of CVD. Cultural differences between the different countries and continents may also have some influence on the measured prevalence. We noticed that female patients visit a GP more frequently in LA compared with A.

The total prevalence of CVD and CVI is highest in EE and lowest in A. After correcting for risk factors, however, these differences are greatly reduced. This emphasizes the importance of risk factors in the development of VD. The most important risk factor is the "positive family history." This suggests that heredity may be an important factor. The role of genetics in CVD remains unclear. Cornu-Thenard et al[24] showed that the risk of developing varicose veins was 90% for children when both parents had varicose veins, 25% for men, and 62% for women when 1 parent was affected. The heritability of CVD is high, which suggests a notable genetic component in the etiology of the disease. However, the genes which are involved are yet to be identified. The precise nature and profile of the genes involved in chronic VD remain a poorly understood entity.[25]

Two important risk factors for developing the VD are age and gender.[11] The fact that older female patients have more advanced VD may explain why only in older female patients a statistical significant difference could be found in the predicted prevalence of CVD (and CVI). In general,

Table 4. Descriptive Table of the Risk Factors, Per Region.[a]

Region	Mean Age (SD) Years	Female Predominance	Number of Births, Mean (SD)	Obesity (BMI >30)	Hours Sitting, Mean (SD)	Hours Standing, Mean (SD)	Positive Family History	Regular Exercise	Smoking (Current or Past)	Birth Control Pills (Females Only)
Asia	46.4 (16.2)	67.42%, 8285/12 288	2.38 (1.98)	15.12%, 1858/12 288	5.43 (2.77)	5.15 (2.75)	19.8%, 2408/12 170	24.2%, 2956/12 225	25.2%, 3065/12 171	13%, 1034/7976
Eastern Europe	54.4 (15.4)	70.70%, 21289/30 110	1.66 (1.07)	27.57%, 8302/30 110	5.78 (2.82)	6.3 (3.04)	46.2%, 13 633/29 530	23.7%, 7125/30 034	41.3%, 12394/29 985	8%, 1634/20 554
Latin America	44.4 (16.1)	73.80%, 7395/10 020	2.07 (2.22)	16.7%, 1673/10020	5.00 (2.80)	7.16 (3.43)	50.3%, 5029/10 004	32.7%, 3269/10 010	30.0%, 2993/9989	20.3%, 1481/7281
Western Europe	53.2 (17.0)	69.58%, 32 661/46 941	1.98 (1.41)	16.74%, 7857/46 941	5.73 (2.69)	6.62 (3.12)	47.3%, 21 936/46 354	42.6%, 19 742/46 341	47.5%, 21 390/46 300	23.7%, 7216/30 463

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]Based on a χ^2 test for gender, obesity, family history, regular exercise, smoking, and birth control pills and a Kruskal-Wallis test for number of births, hours sitting, and hours standing. Risk factors were significantly associated with region ($P < .001$).

Table 5. Predicted Probability Having Chronic Venous Disease (CVD) and Chronic Venous Insufficiency (CVI) for Different Age Groups (Unadjusted for Risk Factors).

Severity Venous Disease	Region	Gender	Predicted Probability (95% CI), 18-34 Years	Predicted Probability (95% CI), (35-50 Years)	Predicted Probability (95% CI), (51-64 Years)	Predicted Probability (95% CI), (>65 Years)
CVD (C1-C6)	Asia	Female	37.8 (25.1-52.3)	57.8 (47.3-67.5)	69.5 (63.3-75.1)	68.8 (59.5-76.8)
	Eastern Europe	Female	45.0 (35.2-55.2)	72.1 (64.1-79)	82.6 (72.8-89.3)	86.6 (79.3-91.7)
	Latin America	Female	57.3 (52.2-62.3)	77.12 (72.9-80.8)	88.3 (76.3-88.6)	88.5 (85.5-91.1)
	Western Europe	Female	38.4 (26.9-51.4)	64.3 (53.1-74.1)	76.9 (69.3-83.2)	84.0 (77.2-89)
	Asia	Male	25.8 (11.6-47.9)	43.5 (24.4-64.8)	48.8 (37.9-59.9)	57.4 (40.8-72.5)
	Eastern Europe	Male	24.2 (15.1-36.4)	50.1 (40-60.1)	70.3 (59.6-79.1)	75.9 (66.0-83.7)
	Latin America	Male	34.9 (26.4-44.5)	54.1 (48.7-59.5)	61.6 (34.7-82.9)	66.0 (51.3-78.3)
	Western Europe	Male	14.3 (7.6-25.1)	33.8 (22.7-47.2)	53.6 (41.3-65.5)	66.0 (60.0-74.2)
CVI (C3-C6)	Asia	Female	7.8 (3.3-17.2)	12.5 (5.9-24.2)	21.9 (12.6-35.1)	22.0 (11.5-38.1)
	Eastern Europe	Female	9.1 (6.5-12.6)	22.3 (17.4-28.3)	33.3 (25.7-41.9)	44.2 (36.9-51.6)
	Latin America	Female	17.5 (8.7-32.3)	35.2 (18.1-57.2)	39.8 (26.9-54.7)	45.6 (36.9-54.5)
	Western Europe	Female	8.7 (2.4-26.7)	14.3 (4.0-40.4)	24.6 (7.1-58.4)	38.7 (15.5-68.4)
	Asia	Male	6.8 (3.9-11.4)	13.1 (7.1-22.9)	17.9 (12.6-24.8)	27.7 (23.3-32.6)
	Eastern Europe	Male	7.0 (4.1-11.8)	17.8 (13.7-22.9)	29.8 (23.0-37.7)	38.5 (31.6-45.8)
	Latin America	Male	9.9 (2.9-28.5)	24.6 (13.9-39.6)	34.1 (22.1-48.0)	33.2 (18.3-52.5)
	Western Europe	Male	3.3 (0.6-16.4)	8.9 (2.5-27.2)	14.2 (3.9-39.9)	29.8 (12.9-54.9)

Abbreviation: 95% CI, 95% confidence interval.

Table 6. Significance of Influence of Risk Factors on the Predicted Probability of Having Chronic Venous Disease (CVD; Mixed Logistic Regression—PROC GLIMMIX).

Risk Factors	18-34 Years	35-50 Years	51-65 Years	>65 Years
Region	$P = .03$	$P = .029$	$P = .21$	$P = .01$
Obesity	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Positive family history	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Regular exercise	$P < .001$	$P < .001$	$P = .007$	$P = .048$
Smoking	$P < .001$	$P = .065$	$P = .890$	$P = .759$
Hours sitting	$P < .001$	$P = .058$	$P = .231$	$P = .003$
Hours standing	$P \leq .002$	$P < .001$	$P = .017$	$P = .022$
Birth control pills	$P = .049$	$P = .005$	$P = .584$	$P = .923$

the power of a logistic regression increases when the proportion of events (and nonevents) approaches 50%. In a population with more VD, it is more likely to find some differences in the predicted probability of having VD between the different regions.

Other important risk factors are the number of pregnancies, obesity, not "having regular exercise," number of hours "sitting" or "standing" each day, and smoking. All risk factors differ significantly between the regions ($P < .001$). Depending on age groups, most of the risk factors also have a significant influence on the prevalence of CVD. This means that modifying these risk factors may have an influence on the prevalence of CVD or even on recurrent VD. This study shows that the highest prevalence of CVD and CVI was measured in EE. However, when calculating the estimated prevalences of CVD and CVI (thus correcting for age and gender), these differences in prevalence decrease. When corrected for other risk factors (smoking, prolonged sitting and standing, not having regular exercise, use of birth control tablets, positive family history for VD, obesity), differences disappear with the exception of CVD in female patients older than 65 years.

This survey also confirms the finding that VD is more common among female patients compared with males and is increasing with age. The VD is a progressive disorder influenced by venous hypertension. Humans are the only mammals that have varicose veins. This can be explained by the fact that humans walk upright. This means that gravity, and thus venous hypertension, plays an important role in the pathogenesis of VD. The fact that Asian people are smaller on average compared with European or Latin American people may be an additional explanation. Indeed, we could find a significant difference in average height between people from different regions. Asian patients (male and female) were significant smaller in height compared with patients of WE and EE (both $P < .001$). However, the difference in stature (height) between Asian patients and patients of LA was not significant ($P = .37$ males; $P = .54$ females). Other possible causes of the measured lower prevalence of VD in older Asian patients can be due to other differences in way of life, environmental factors, and food. A Western diet, having a lack of fibers, induces constipation. This can cause small intra-abdominal pressure increase which then obstructs venous return from the legs. Constipation and resultant straining cause an inherent increase in intra-abdominal pressure, which over time can lead to dilatation or other changes in both superficial and deep venous system of the leg.[26] Since "having a positive family history of CVD" is an important and significant risk factor, genetics may have an important influence in the development of CVD.

Conclusions

Chronic venous disease is very common worldwide. Its prevalence differs between different geographical areas. However, most of this variation in prevalence can be explained by differences in risk factors. After correcting for risk factors, the differences in estimated prevalence among the different regions diminish. This emphasizes the influence of the risk factors on the development of VD.

Table 7. Estimates (as Odds Ratios and 95% CI) and Significance (*P* Value) in Difference Between Regions, Unadjusted, and Adjusted for Risk Factors, in Probability Having Chronic Venous Disease (CVD) for Female Patients (Age Groups: 51-64 and >65 Years).

Age/Gender	Region	Versus	Estimate Unadjusted Analysis OR (95% CI)	*P*	Estimate Adjusted for Risk Factors OR (95% CI)	*P*
Female (51-64 years)	Asia	Eastern Europe	0.468 (0.253-0.863)	.018	0.648 (0.344-1.221)	.1681
	Asia	Latin America	0.443 (0.263-0.746)	.004	0.606 (0.344-1.069)	.081
	Asia	Western Europe	0.677 (0.415-1.104)	.111	0.961 (0.562-1.645)	.88
	Eastern Europe	Latin America	0.947 (0.466-1.925)	.874	0.936 (0.471-1.860)	.843
	Eastern Europe	Western Europe	1.447 (0.728-2.874)	.274	1.484 (0.765-2.877)	.227
	Latin America	Western Europe	1.527 (0.834-2.798)	.159	1.585 (0.872-2.879)	.123
Female (>65 years)	Asia	Eastern Europe	0.331 (0.165-0.665)	.018	0.424 (0.198-0.906)	.029
	Asia	Latin America	0.287 (0.167-0.492)	.004	0.319 (0.168-0.606)	.002
	Asia	Western Europe	0.411 (0.211-0.800)	.111	0.540 (0.244-1.195)	.121
	Eastern Europe	Latin America	0.865 (0.464-1.613)	.874	0.752 (0.429-1.319)	.302
	Eastern Europe	Western Europe	1.241 (0.596-2.585)	.274	1.274 (0.613-2.645)	.496
	Latin America	Western Europe	1.434 (0.797-2.581)	.159	1.693 (0.922-3.106)	.085

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Authors' Note

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