Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study

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Summary

Background Estimation of the epidemiological burden of carotid atherosclerosis can serve as a basis for prevention and management of cardiovascular disease. We aimed to provide the first estimation on the prevalence, number of cases, and risk factors for carotid atherosclerosis in the general population globally and regionally.

Methods In this systematic review, meta-analysis, and modelling study, we searched PubMed, MEDLINE, Embase, Global Health, and China National Knowledge Infrastructure for articles published from database inception until May 7, 2019, with no language restrictions, for population-based studies that quantified prevalence of carotid atherosclerosis by means of increased carotid intima-media thickness, carotid plaque, and carotid stenosis. Studies were eligible if they included bilaterally scanned carotid arteries using ultrasonography and defined increased carotid intima-media thickness as a thickness of 1·0 mm or more, carotid plaque as a focal carotid intima-media thickness of 1·5 mm or more encroaching into the lumen or at least 0·5 mm or 50% compared with the surrounding carotid intima-media thickness values, and carotid stenosis as 50% or more stenosis. Studies were excluded if the sample was not representative of the general population. We also included studies identified in our previous systematic review and meta-analysis of the prevalence of carotid atherosclerosis in China. We estimated age-specific and sex-specific prevalences of increased carotid intima-media thickness, carotid plaque, and carotid stenosis. We used UN population data to generate the number of people affected in 2000, 2015, and 2020. We did random-effects meta-analyses to assess the effects of risk factors for increased carotid intima-media thickness and carotid plaque. We derived regional numbers of people living with increased carotid intima-media thickness and carotid plaque in 2015 using a risk factors-based model by WHO region. All analyses were done in populations aged 30–79 years due to availability of data. This systematic review and meta-analysis is registered online on PROSPERO, CRD42019134709.

Findings We identified 8632 articles through our database search, of which 515 were eligible for full-text review, including 37 articles from our previous study, and 59 articles were eligible for inclusion in our systematic review and meta-analysis. Overall, in people aged 30–79 years in 2020, the global prevalence of increased carotid intima-media thickness is estimated to be 27·6% (95% CI 16·9–41·3), equivalent to 1066·70 million affected people and a percentage change of 57·46% from 2000; of carotid plaque is estimated to be 21·1% (13·2–31·5), equivalent to 815·76 million affected people and a percentage change of 58·97% from 2000; and carotid stenosis is estimated to be 1·5% (1·1–2·1), equivalent to 57·79 million affected people and a percentage change of 59·13% from 2000. The prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis increased consistently with age and was higher in men than in women. Current smoking, diabetes, and hypertension were common risk factors for increased carotid intima-media thickness and carotid plaque. In 2015, the Western Pacific region had the largest share of global cases of increased carotid intima-media thickness (317·62 million [33·36%] of 952·13 million affected people) and carotid plaque (240·77 million [33·20%] of 725·25 million), whereas the African region had the smallest share of cases of increased carotid intima-media thickness (59·08 million [6·21%]) and the Eastern Mediterranean region had the smallest share of carotid plaque cases (44·59 million [6·15%]).

Interpretation A substantial global burden of carotid atherosclerosis exists. Effective strategies are needed for primary prevention and management of carotid atherosclerosis. High-quality epidemiological investigations on carotid atherosclerosis are needed to better address the global burden of carotid atherosclerosis at finer levels.

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See **Comment** page e625

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Introduction

Cardiovascular disease has become a leading cause of disability and premature mortality globally.[1–3] According to the Global Burden of Diseases, Injuries, and Risk Factor Study 2015, cardiovascular disease affected an estimated 422·7 million people and caused an estimated 17·9 million deaths worldwide in 2015, comprising 31% of all global deaths.[1,4] Cardiovascular diseases are not only

Research in context

Evidence before this study

An up-to-date understanding of the burden of carotid atherosclerosis worldwide is imperative for developing effective strategies for primary prevention and management and to inform stakeholders. However, to our knowledge, no current estimation on the prevalence of carotid atherosclerosis is available at the global level.

Added value of this study

To our knowledge, we provide the first robust prevalence estimates of carotid atherosclerosis in the general population at both the global and regional levels based on 59 articles published up to 2019. The prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis increased with older age and was higher in men than in women. In 2020 in people aged 30–79 years worldwide, the prevalence of increased carotid intima-media thickness is estimated to be 27·62%, equivalent to 1066·70 million cases, of carotid plaque was 21·13%, equivalent to 815·76 million cases, and of carotid stenosis was 1·50%, equivalent to 57·79 million cases.

Implications of all the available evidence

Increased carotid intima-media thickness and carotid plaque are common disorders in the general population. The large numbers of people living with carotid plaque and carotid stenosis worldwide is a considerable public health concern. This study is expected to prompt further epidemiological studies on carotid atherosclerosis.

diseases of high-income countries. In the past few decades, the burden of cardiovascular disease has grown disproportionally in low-income and middle-income countries, where over 80% of cardiovascular disease deaths now occur.[3,5] By 2030, approximately 23·6 million people are predicted to die from cardiovascular diseases annually.[6] The huge and still growing burden of cardiovascular diseases on individuals, families, and health-care systems indicates an urgent need for research on atherosclerotic diseases and implementation of preventive measures.

Atherosclerosis, the main pathological process of most cardiovascular diseases, can begin early in life and remain latent and asymptomatic for long periods before progressing into its advanced stages.[7,8] Early detection of atherosclerosis in apparently healthy people has mainly focused on peripheral arteries and carotid arteries.[9] Using ultrasonography, carotid intima-media thickness can be assessed non-invasively.[10,11] According to the 2016 European guidelines on cardiovascular disease prevention in clinical practice, a carotid intima-media thickness of 1·0 mm or more is generally considered to be abnormal.[9] The Mannheim Carotid Intima-Media Thickness Consensus also suggested that advanced stages of atherosclerosis, including plaque, stenosis, and occlusion, are indicators of cardiovascular risk.[10] Via a systematic review, meta-regression, and individual-participant data meta-analysis, de Weerd and colleagues[12,13] established the global prevalence of moderate (≥50% stenosis) and severe (≥70% stenosis) carotid stenosis in asymptomatic people.

See Online for appendix

An up-to-date understanding of the worldwide burden of carotid atherosclerosis is imperative for developing effective strategies for primary prevention and management and informing stakeholders. However, no current estimates of the prevalence of carotid atherosclerosis are available at the global level. To fill this gap in knowledge, we did a systematic review of epidemiological studies that reported the prevalence of carotid atherosclerosis in the general population. We aimed to provide the age-specific and sex-specific prevalence of carotid atherosclerosis, establish the main risk factors for carotid atherosclerosis, estimate the global number of people living with carotid atherosclerosis from 2000 to 2020, and generate the regional number of people affected by carotid atherosclerosis in 2015, the most recent year with available data.

Methods

Search strategy and selection criteria

In this systematic review, meta-analysis, and modelling study, two investigators (ZF and HW) independently did a comprehensive literature search to identify all epidemiological studies that reported the prevalence of three carotid atherosclerotic disorders—namely, increased carotid intima-media thickness, carotid plaque, and carotid stenosis—in the general population. They searched four bibliographic databases—PubMed, MEDLINE, Embase, and Global Health—from database inception until May 7, 2019, using a combination of terms related to carotid atherosclerosis and prevalence without restrictions on language or publication date; complete details of the search strategies are in the appendix (p 4). Studies were eligible if they were population-based studies that included bilaterally scanned carotid arteries using ultrasonography and defined increased carotid intima-media thickness, carotid plaque, or carotid stenosis in a standardised manner according to the 2016 European guidelines on cardiovascular disease prevention in clinical practice guideline or the Mannheim Carotid Intima-Media Thickness Consensus.[9,10] These guidelines defined increased carotid intima-media thickness as a thickness of 1·0 mm or more, carotid plaque as a focal carotid intima-media thickness of 1·5 mm or more encroaching into the lumen or at least 0·5 mm or 50% compared with the surrounding carotid intima-media thickness values, and carotid stenosis as 50% or more stenosis, including occlusion.[9,10,14] Studies were excluded if they had been

done in people who were not representative of the general population (eg, people with specific diseases, individuals free from cardiovascular diseases [asymptomatic individuals]).

In 2018, we did a study on the prevalence of carotid atherosclerosis in China through a systematic review and meta-analysis (the China Carotid Atherosclerosis Study),[14] in which epidemiological studies on the prevalence of increased carotid intima-media thickness and carotid plaque in the general Chinese population were included. The 37 articles in the China Carotid Atherosclerosis Study were assessed in our full-text review. For the present systematic review, we updated our previous search in the China Carotid Atherosclerosis Study using the largest Chinese bibliographic source, China National Knowledge Infrastructure, searching for publications from April 15, 2017, until May 8, 2019. This updated search of the Chinese literature was also restricted to epidemiological studies investigating the prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis in the general Chinese population; the full search strategy is in the appendix (p 4).

Additionally, all coauthors did manual searches of the reference lists of the included articles and individually identified review articles on the topic to identify additional eligible articles. We did not search the grey literature or conference abstracts.

Two investigators (PS and YZ) independently reviewed abstracts and full-text articles using the prespecified eligibility criteria. If multiple articles provided data from the same investigation, we included the one with the largest sample size. Conflicts were resolved by consensus through group discussions.

The protocol for this study is available online.

Data analysis

The following information from the included articles was independently extracted by two investigators (PS and YZ): first author, publication year, geographical location of investigation, regions of study location (African region, region of the Americas, South-East Asia region, European region, Eastern Mediterranean region, and Western Pacific region, as designated by WHO; high-income countries and low-income and middle-income countries, as designated by the World Bank for 2019–20), study design, investigation date, sample size, average age of participants, proportion of female participants, diagnostic method, definition of disease (increased carotid intima-media thickness, carotid plaque, or carotid stenosis), and number of cases. Data were extracted manually. For articles in which potential risk factors were explored using multivariable logistic regressions, the definitions of each risk factor and the reported odds ratio (OR) were also extracted. In articles where the year of investigation was not specifically presented, we assigned it as 5 years before the publication year (the mean time-lag between investigation and publication based on articles with available data; appendix pp 5–6).

To assess the quality of included articles, we used a quality scale based on the Strengthening the Reporting of Observational Studies in Epidemiology statement.[15] The quality of each article was rated by two independent investigators (PS and YZ) on the basis of five modules: sample population, sample size, participation rate, outcome assessment, and analytical methods. Each module was assigned a score of 0–2, representing low, moderate, and high quality. The overall score out of ten is indicative of the overall quality (appendix p 7).

Any discrepancies in these data extraction and quality assessment stages were resolved by consensus through group discussions.

Statistical analysis

We did this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] We did all analyses of increased carotid intima-media thickness, carotid plaque, and carotid stenosis separately. To derive a robust estimation, we restricted prevalence and number of cases to the age range 30–79 years, a range for which a comprehensive number of datapoints were available.

First, we did an epidemiological modelling analysis to determine the prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis. 36 of 59 articles included in our analysis provided multiple datapoints (age-specific or sex-specific prevalence). To use all information to the fullest, we used a multilevel mixed-effects meta-regression approach.[17,18] To control the effects of multiple datapoints from the same study and multiple studies from the same country, the study identification number we allocated to each study, and country identification were added into the regression model as the random effect (u_i).[19] Given that prevalence (p)=number of participants with condition / total number of participants, we stabilised the prevalence with the logit link as follows

For the **protocol** see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=134709

$$\begin{aligned}\text{logit}(p) &= (\text{In}(p / [1-p]) \\ &= \text{In}(\text{odds}) \\ &= \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + u_i\end{aligned}$$

where α is the intercept term, β is the coefficient, and x is the variable.

We first assessed the effects of cluster-level variables x_1–x_n, including age, proportion of participants that were female, setting (rural, urban, and mixed), income region (high-income countries and low-income and middle-income countries), and investigation period (before 2000, 2000–09, and 2010 and after) due to availability of relevant information by a univariable metaregression (appendix pp 8–9). From this analysis, we identified that age and

proportion of participants were female were significantly associated with the prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis; therefore we amended our calculation to

$$\text{logit}(p) = \alpha + \beta_1 \text{age} + \beta_2 \text{female proportion} + u_i$$

then,

$$p = \frac{\exp(\alpha + \beta_1 \text{age} + \beta_2 \text{female proportion} + u_i)}{1 + \exp(\alpha + \beta_1 \text{age} + \beta_2 \text{female proportion} + u_i)}.$$

We estimated the age-specific and sex-specific prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis using this model.

Second, we estimated the global numbers of people with increased carotid intima-media thickness, carotid plaque, and carotid stenosis for 2000, 2015, and 2020. We generated these numbers by multiplying the estimated age-specific and sex-specific prevalences by the corresponding world populations in 2000, 2015, and 2020, obtained from the UN Population Division.[20]

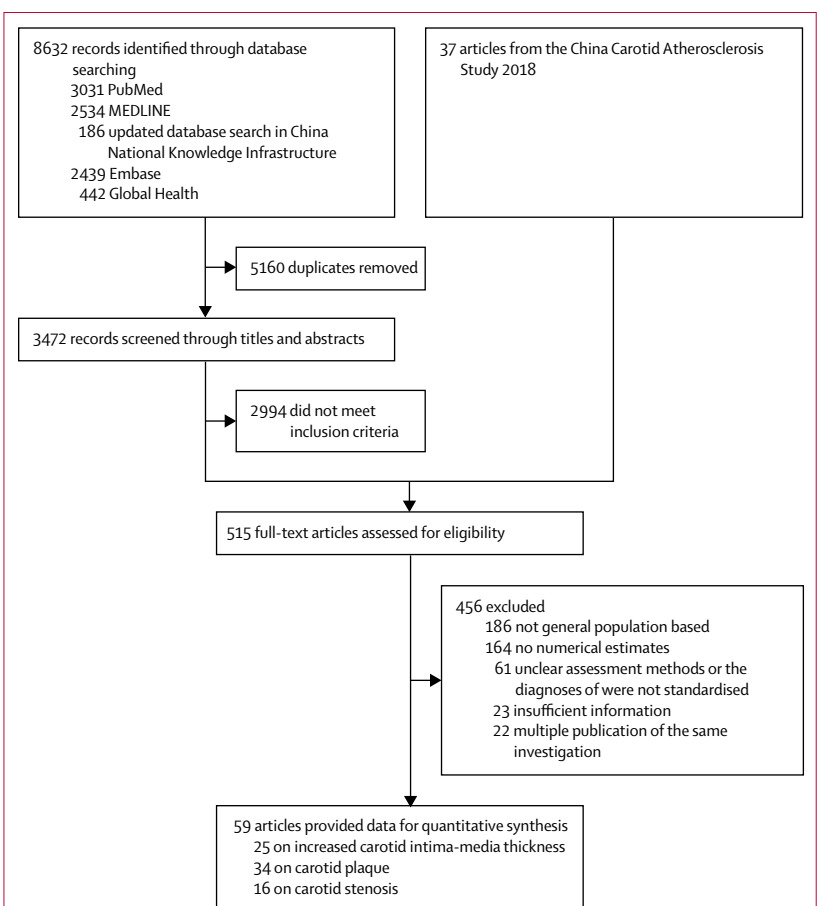

Figure 1: **Study selection**

Third, we did a meta-analysis of risk factors for increased carotid intima-media thickness and carotid plaque. A subset of included articles explored potential risk factors for increased carotid intima-media thickness, carotid plaque, and carotid stenosis. We only included risk factors that had been assessed in at least three investigations using multivariable logistic regressions in our meta-analysis. We used a random-effects (DerSimonian and Laird method) meta-analysis to synthesise the effects of binary and continuous risk factors.[17] Due to data availability, this process was only done for increased carotid intima-media thickness and carotid plaque. For binary variable risk factors, we estimated odds ratios (ORs) that indicate the risk of increased carotid intima-media thickness or carotid plaque compared with those without the risk factor, except for current alcohol drinkers, for whom the comparator was never drinkers; former smokers, for whom the comparator was never smokers; and current smokers, for whom the comparator was never smokers.

Finally, we estimated the number of people with increased carotid intima-media thickness and carotid plaque in 2015 regionally. In line with the China Carotid Atherosclerosis Study and our previous studies,[14,21] we used a risk-factor-based approach and selected three common risk factors for increased carotid intima-media thickness and carotid plaque: current smoking, hypertension, and diabetes. To derive the number of people living with increased carotid intima-media thickness and carotid plaque by region in this risk-factor-based model,[14,21] we obtained the latest prevalence data of current smoking (in 2015), hypertension (in 2015), and diabetes (in 2015) from the WHO report on the global tobacco epidemic and the WHO Global Health Observatory data repository.[22–25] More details on our approaches to estimating the prevalence, number of cases, and risk factors are shown in the appendix (pp 3, 46).

We did all analyses using Stata (version 14.0) and R (version 3.3.0). This systematic review and meta-analysis is registered online on PROSPERO, CRD42019134709.

Role of the funding source

There was no funding source for this study.

Results

We identified 8632 items in our initial literature search. After inclusion of 37 additional articles from the China Carotid Atherosclerosis Study 2018 and removal of duplicates and apparently irrelevant records, we examined 515 full-text articles (figure 1). After full-text screening, 59 articles covering 21 countries (the geographical locations of which are shown in the appendix [p 47]) fulfilled the inclusion criteria, among which 25 articles reported prevalence data on increased carotid intima-media thickness, 34 on carotid plaque, and 16 on carotid stenosis. The characteristics of each study are shown in the appendix (pp 10–26).

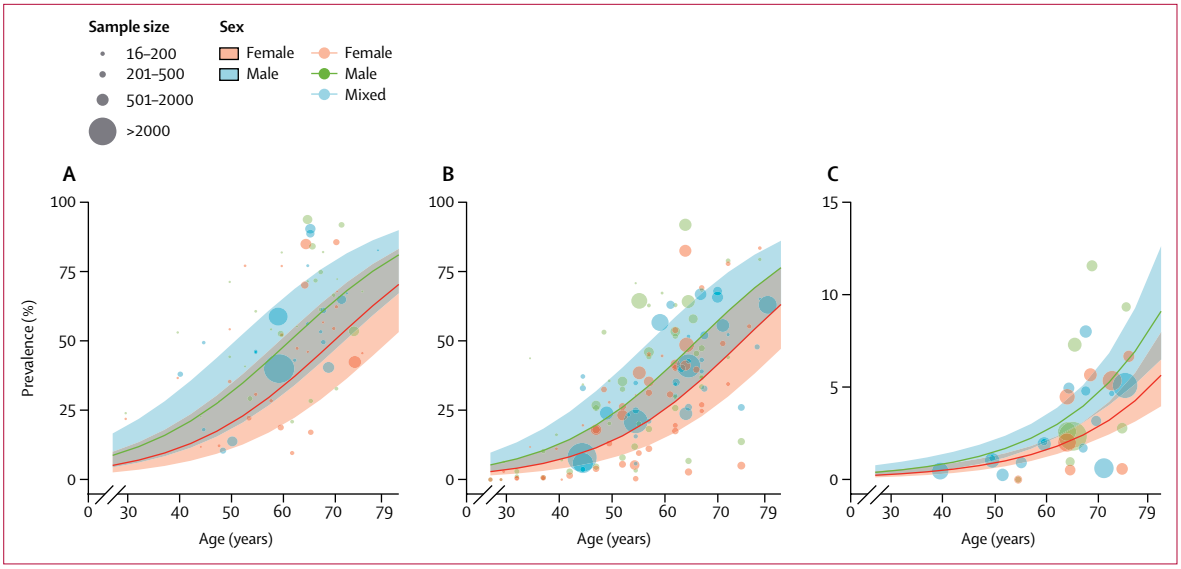

Figure 2: **Age-specific and sex-specific prevalence of increased carotid intima-media thickness (A), carotid plaque (B), and carotid stenosis (C) for people aged 30–79 years**

Solid lines are prevalence estimates, with shaded areas indicating 95% CIs. Each circle represents a contributing datapoint. Mixed-sex data are from studies that reported the proportions of male and female participants but only combined prevalence estimate. For increased carotid intima-media thickness and carotid stenosis, the regression lines at younger (<40 years) and older (>75 years) age groups are based on few datapoints or projection only. For carotid stenosis, to make the plot readable, the study by Savji and colleagues[26] was removed when drawing the plot due to its overwhelmingly large sample size influence.

	Increased carotid intima-media thickness		Carotid plaque		Carotid stenosis	
	Men	Women	Men	Women	Men	Women
30–34 years	11·7% (6·0–21·7)	6·9% (3·4–13·4)	7·5% (4·0–13·5)	4·1% (2·2–7·6)	0·5% (0·3–1·0)	0·3% (0·2–0·6)
35–39 years	15·8% (8·3–28·1)	9·4% (4·8–17·9)	10·5% (5·7–18·3)	5·8% (3·1–10·6)	0·7% (0·4–1·2)	0·4% (0·2–0·7)
40–44 years	21·0% (11·3–35·6)	12·9% (6·6–23·5)	14·5% (8·1–24·5)	8·2% (4·5–14·7)	0·9% (0·6–1·5)	0·6% (0·4–0·9)
45–49 years	27·3% (15·3–43·8)	17·3% (9·1–30·2)	19·7% (11·3–31·9)	11·5% (6·3–19·9)	1·3% (0·8–1·9)	0·8% (0·5–1·1)
50–54 years	34·7% (20·4–52·4)	22·8% (12·5–37·9)	26·1% (15·6–40·4)	15·8% (8·9–26·4)	1·7% (1·2–2·4)	1·0% (0·7–1·4)
55–59 years	42·9% (26·6–60·8)	29·5% (16·8–46·4)	33·9% (21·1–49·5)	21·3% (12·4–34·2)	2·2% (1·7–3·0)	1·3% (1·0–1·8)
60–64 years	51·5% (33·9–68·7)	37·1% (22·2–55·0)	42·5% (27·9–58·6)	28·1% (17·0–42·9)	3·0% (2·3–3·9)	1·8% (1·4–2·4)
65–69 years	60·0% (42·0–75·7)	45·5% (28·7–63·4)	51·7% (35·8–67·2)	36·2% (22·8–52·1)	4·0% (3·1–5·1)	2·4% (1·9–3·1)
70–74 years	68·0% (50·6–81·5)	54·2% (36·3–71·0)	60·8% (44·7–74·8)	45·0% (30·0–61·1)	5·3% (4·0–6·8)	3·2% (2·4–4·2)
75–79 years	75·0% (59·1–86·2)	62·6% (44·5–77·7)	69·1% (53·9–81·1)	54·2% (38·2–69·4)	6·9% (5·2–9·3)	4·3% (3·1–5·8)
Overall (30–79 years) in 2020	32·1% (20·2–46·7)	23·2% (13·7–35·9)	25·2% (16·1–36·7)	17·1% (10·4–26·5)	1·8% (1·3–2·6)	1·2% (0·8–1·6)

Data are prevalence, with 95% CIs in parentheses.

Table 1: **Estimated prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis in people aged 30–79 years, by age group and sex**

45 (76%) of 59 included articles were published in the past decade (2010–19), and 34 (58%) were done in rural–urban mixed settings. Additionally, 21 (36%) articles provided age-specific prevalences and 30 (51%) provided sex-specific prevalences. 28 (47%) articles were done in high-income countries and the other 31 (53%) were in low-income and middle-income countries. All the 59 articles had a quality score of six or above. The results of detailed quality assessments are in the appendix (pp 27–28).

Based on the available datapoints from the included articles, the sex-specific associations between age and prevalence are shown in figure 2. Generally, the prevalence of increased carotid intima-media thickness, carotid plaque, and carotid stenosis all increased with increasing age. The age-specific and sex-specific prevalence estimates of increased carotid intima-media thickness, carotid plaque, and carotid stenosis are shown in table 1. For increased carotid intima-media thickness, carotid plaque, and carotid stenosis, women consistently had lower prevalence than men over the whole age range covered by available datapoints and of research interest (30–79 years). In 2020, the prevalence of increased carotid intima-media

	Increased carotid intima-media thickness			Carotid plaque			Carotid stenosis		
	2000 (millions)	2020 (millions)	Percentage change (%)	2000 (millions)	2020 (millions)	Percentage change (%)	2000 (millions)	2020 (millions)	Percentage change (%)
30–34 years	44·56 (22·45–84·20)	56·56 (28·50–106·86)	26·93%	27·80 (14·92–50·50)	35·30 (18·94–64·11)	26·96%	2·00 (1·08–3·68)	2·54 (1·38–4·68)	26·92%
35–39 years	54·21 (27·96–98·73)	69·02 (35·60–125·70)	27·32%	35·02 (19·05–62·20)	44·59 (24·25–79·20)	27·33%	2·40 (1·40–4·11)	3·06 (1·78–5·24)	27·32%
40–44 years	63·38 (33·64–110·54)	83·73 (44·44–146·03)	32·10%	42·52 (23·55–73·37)	56·17 (31·11–96·92)	32·10%	2·81 (1·76–4·48)	3·71 (2·32–5·92)	32·10%
45–49 years	75·02 (41·21–124·50)	106·96 (58·76–177·52)	42·59%	52·40 (29·71–87·23)	74·72 (42·37–124·38)	42·59%	3·38 (2·26–5·05)	4·82 (3·22–7·20)	42·59%
50–54 years	76·03 (43·50–119·47)	128·08 (73·30–201·23)	68·46%	55·43 (32·38–88·38)	93·39 (54·57–148·89)	68·48%	3·55 (2·51–5·01)	5·98 (4·24–8·44)	68·49%
55–59 years	75·63 (45·38–112·12)	140·08 (84·06–207·63)	85·21%	57·64 (34·96–87·47)	106·77 (64·76–162·00)	85·23%	3·75 (2·78–5·04)	6·94 (5·16–9·33)	85·24%
60–64 years	83·24 (52·64–116·37)	142·23 (89·96–198·78)	70·86%	66·30 (42·02–95·35)	113·29 (71·81–162·91)	70·89%	4·48 (3·44–5·84)	7·67 (5·88–9·98)	70·92%
65–69 years	80·29 (53·69–106·05)	141·47 (94·66–186·78)	76·21%	66·69 (44·42–90·77)	117·56 (78·33–159·93)	76·27%	4·82 (3·73–6·21)	8·50 (6·58–10·95)	76·39%
70–74 years	71·58 (50·64–89·78)	114·27 (80·94–143·18)	59·64%	61·77 (43·36–79·72)	98·69 (69·36–127·23)	59·77%	4·89 (3·74–6·38)	7·83 (5·99–10·22)	60·11%
75–79 years	53·37 (39·84–63·99)	84·28 (63·10–100·83)	57·92%	47·60 (35·21–58·52)	75·29 (55·87–92·35)	58·20%	4·23 (3·13–5·68)	6·73 (4·98–9·05)	59·31%
Overall (30–79 years)	677·32 (410·96–1025·74)	1066·70 (653·30–1594·52)	57·49%	513·16 (319·58–773·52)	815·76 (511·36–1217·93)	58·97%	36·32 (25·83–51·50)	57·79 (41·52–81·02)	59·13%

Data are number of people, in millions, with 95% CI in parentheses, unless otherwise stated.

Table 2: **Estimated number of people with increased carotid intima-media thickness, carotid plaque, and carotid stenosis worldwide in 2000 and 2020 and the percentage change from 2000 to 2020**

	Number of studies	Odds ratio (95% CI)	z value	p value
Increased carotid intima-media thickness				
Risk factor 1: age, per 10-year increase	4	2·71 (2·07–3·55)	7·26	<0·001
Risk factor 2: female sex	5	0·49 (0·38–0·64)	5·43	<0·001
Risk factor 3: current smoker	5	1·76 (1·34–2·30)	4·11	<0·001
Risk factor 4: current alcohol drinker	3	0·94 (0·70–1·26)	0·41	0·680
Risk factor 5: diabetes	4	2·23 (1·48–3·36)	3·82	<0·001
Risk factor 6: hypertension	5	1·55 (1·03–2·34)	2·08	0·038
Risk factor 7: dyslipidaemia	3	0·90 (0·65–1·25)	0·61	0·542
Carotid plaque				
Risk factor 1: age, per 10-year increase	4	1·79 (0·93–3·43)	1·76	0·079
Risk factor 2: female sex	5	0·55 (0·33–0·94)	2·20	0·028
Risk factor 3: former smoker	3	1·58 (1·06–2·36)	2·26	0·024
Risk factor 4: current smoker	5	1·70 (1·41–2·04)	5·64	<0·001
Risk factor 5: diabetes	3	1·45 (1·12–1·90)	2·77	0·006
Risk factor 6: hypertension	3	1·75 (1·44–2·13)	5·56	<0·001
Risk factor 7: systolic blood pressure, per 10 mm Hg increase	3	1·11 (1·08–1·15)	6·50	<0·001
Risk factor 8: HDL, per mmol/L increase	3	0·46 (0·21–0·99)	1·98	0·048
Risk factor 9: BMI, per kg/m^2 increase	4	0·97 (0·91–1·02)	1·15	0·249

The definitions of some risk factors varied slightly across studies. Odds ratios for binary variable risk factors indicated the risk of increased carotid intima-media thickness or carotid plaque compared with those without the risk factor, except for current alcohol drinkers (*vs* never drinkers), former smokers (*vs* never smokers), and current smokers (*vs* never smokers). BMI=body-mass index.

Table 3: **Synthesised effect size of risk factors for increased carotid intima-media thickness and carotid plaque**

thickness in people aged 30–79 years is estimated to be 27·6% (95% CI 16·9–41·3), of carotid plaque is estimated to be 21·1% (13·2–31·5), and of carotid stenosis is estimated to be 1·5% (1·1–2·1).

The numbers of people living with increased carotid intima-media thickness, carotid plaque, and carotid stenosis in 2000 and 2020 are shown in table 2. Due to demographic ageing during 2000–20, the number of people with increased carotid intima-media thickness increased by 57·49%, with carotid plaque increased by 58·97%, and with carotid stenosis increased by 59·13% over this period. For increased carotid intima-media thickness, carotid plaque, and carotid stenosis, the age group in which percentage change was the highest (at approximately 85%) was 50–59 years.

We assessed the effects of seven risk factors for increased carotid intima-media thickness, and nine risk factors for carotid plaque in a meta-analysis (table 3). Older age, male sex, current smoking, diabetes, and hypertension were associated with an increased risk of increased carotid intima-media thickness. For carotid plaque, the significant risk factors were male sex, former smoking, current smoking, diabetes, hypertension, a higher level of systolic blood pressure, and a lower level of HDL. The individual articles that contributed to these meta-analyses are listed in the appendix (pp 29–44).

The numbers of people affected by increased carotid intima-media thickness and carotid plaque in the

six WHO regions in 2015 are shown in figure 3 and detailed in the appendix (p 45). The Western Pacific region had the largest share of global cases of increased carotid intima-media thickness (317·62 million [95% CI 194·71–473·73; 33·36%] of 952·13 million) and of carotid plaque (240·77 million [95% CI 150·96–359·22; 33·20%] of 725·25 million). The African region had the smallest share of cases of increased carotid intima-media thickness (59·08 million [34·91–92·19; 6·21%) and the Eastern Mediterranean region had the smallest share of cases of carotid plaque (44·59 million [27·36–68·44; 6·15%]). The age groups that contributed the most cases of increased carotid intima-media thickness and carotid plaque were 50–59 years for the African region, South-East Asia region, and Eastern Mediterranean region, and 60–69 years for the region of the Americas, European region, and Western Pacific region (figure 3).

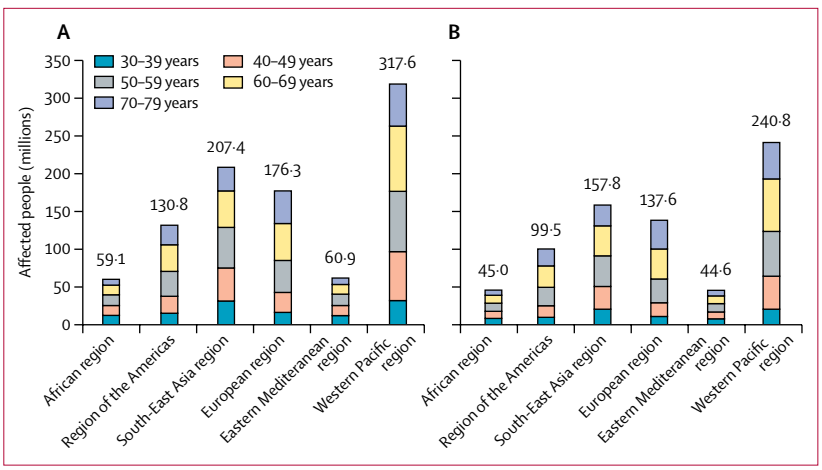

Figure 3: **Regional number of people with increased carotid intima-media thickness (A) and carotid plaque (B), by contributing age groups, in 2015**
People with increased carotid intima-media thickness and carotid plaque were restricted to those aged 30–79 years.

Discussion

Worldwide, we found that approximately 28% of individuals aged 30–79 years in the general population in 2020 had an abnormal carotid intima-media thickness of 1·0 mm and above, translating to just over one billion people. Additionally, approximately 21% of people aged 30–79 years had carotid plaque and 1·5% had carotid stenosis, equivalent to approximately 816 million people with carotid plaque and 58 million with carotid stenosis. Increased carotid intima-media thickness, carotid plaque, and carotid stenosis were more common in older people than in younger people, and in men than in women. Current smoking, diabetes, and hypertension were confirmed as common risk factors for both increased carotid intima-media thickness and carotid plaque. At the regional level in 2015, approximately a third of global cases of increased carotid intima-media thickness and carotid plaque were in the Western Pacific region, whereas the African region had the smallest share of cases of increased carotid intima-media thickness and the Eastern Mediterranean region had the smallest share of cases of carotid plaque, highlighting substantial variations in prevalence worldwide.

As shown in our meta-regression, increased carotid intima-media thickness, carotid plaque, and carotid stenosis were more common in older people than in younger people, which reinforces the hypothesis that atherosclerosis is a chronic disease process of the artery that manifests more commonly as people age.[7,8] Carotid intima-media thickness measures the structural changes in the carotid arterial walls, and could be a marker of early-stage systemic atherosclerosis and smooth muscle hypertrophy or hyperplasia.[9] In our study, we defined increased carotid intima-media thickness as a thickness of 1·0 mm or more. Although a carotid intima-media thickness of 1·0 mm or more is considered to be abnormal, some increased carotid intima-media conditions are clinically benign and might not progress to cardiovascular events.[9,27,28] The 2016 European guidelines on cardiovascular disease prevention in clinical practice do not recommend the implementation of measurements of carotid intima-media thickness in daily clinical practice and routinely in cardiovascular risk assessment.[9] Our estimation of over one billion cases of increased carotid intima-media thickness worldwide should not create unnecessary anxiety among stakeholders. Other advanced-stage phenotypes of carotid atherosclerosis—namely, carotid plaque or carotid stenosis—are associated with increased carotid intima-media thickness but are indicative of different predictive values for cardiovascular diseases.[22,29,30] Previous studies have suggested that people with carotid plaque or carotid stenosis are at an increased risk of developing cardiovascular diseases.[10,23,29] The systematic detection of carotid plaque has been recommended in assessing cardiovascular risk.[9] Given the fact that atherosclerosis is a diffuse disease of arteries, people with carotid atherosclerosis are more likely to have atherosclerotic diseases in other arterial beds—eg, peripheral artery disease and coronary heart disease.[24,25] The large number of people we estimate to be living with carotid plaque or carotid stenosis is indicative of a sizeable number of potential cardiovascular events and therefore a huge burden of diseases on the global health-care system.[10,23]

In line with the meta-analysis by de Weerd and colleagues[12,13] and previous investigations,[31,32] our analysis also noted a clear predominance in carotid atherosclerosis in men. This widely accepted pattern of reduced cardiovascular risk in women might be conferred by the protective role of oestrogens in endothelial function and lipid homoeostasis.[33–35] We identified smoking, diabetes, and hypertension as significant risk factors for increased carotid intima-media thickness and carotid plaque in our meta-analyses, which agrees with previous epidemiological investigations.[36–38] Early detection and management of

diabetes and hypertension might help to slow the progression of atherosclerotic complications and much attention should be paid to subpopulations that are especially vulnerable—eg, men, smokers, people with established cardiovascular diseases.[9] For carotid plaque, we identified the effects of both current smoking and former smoking, with former smoking having a reduced OR in our meta-analysis compared with current smoking. The difference between these two risk factors implies the potential benefits of smoking cessation in reducing the risk of carotid plaque.[38,39] For carotid plaque, a reduced level of HDL was found to be a significant risk factor, which agrees with previous evidence.[40] However, we did not assess the association between increased carotid intima-media thickness and the level of HDL due to a lack of relevant data, as was also the case for different lipids on increased carotid intima-media thickness, carotid plaque, and carotid stenosis. More studies are needed on the association between lipid profile and carotid atherosclerosis.

To the best of our knowledge, this study is the first to derive robust prevalence estimates of carotid atherosclerosis in the general population at both global and regional levels to inform policy makers of the epidemiological magnitude and profile of this public health issue. A strength of this study is that we adopted the standardised definitions of carotid atherosclerosis, including increased carotid intima-media thickness, carotid plaque, and carotid stenosis, before pooling prevalence estimates from different studies, which reduced the uncertainty of our estimation due to differing case definitions.[9] Benefiting from a comprehensive search strategy and dual review process, we included 59 articles in our modelling analysis. Sufficient data from the included articles enabled us to provide the broadest research scope to date of the epidemiological distribution of increased carotid intima-media thickness, carotid plaque, and carotid stenosis simultaneously. We successfully provided prevalence estimates of increased carotid intima-media thickness, carotid plaque, and carotid stenosis by age and sex. In the assessments of the effect of potential risk factors, we only included factors that were reported on the basis of multivariable logistic regressions. This strict inclusion criterion could help to avoid the suspected bias caused by univariable logistic regression.[21]

Our study has several limitations. The first crucial limitation is the deficiency of information on risk factors. For increased carotid intima-media thickness, we were only able to explore the effects of seven potential risk factors and for carotid plaque only nine potential risk factors. The lack of information on risk factors for carotid stenosis restricted our ability to do a risk factor meta-analysis assessment for this condition. Furthermore, we were not able to establish the effects of many important risk factors or covariates of increased carotid intima-media thickness, carotid plaque, and carotid stenosis—such as hypercholesterolaemia, obesity, and physical exercise. A second limitation was that in the distribution of regional cases, we only accounted for demographic structures (age and sex) and the exposure levels of three risk factors (current smoking, diabetes, and hypertension) in different geographical regions on the basis of a risk-factor-based model. Previous studies have suggested that the prevalence of carotid atherosclerosis might be lower in people who are Asian than in those in other ethnic groups; however, we were not able to assess the possible ethnic disparity because of the restricted availability of relevant information.[31,41] We were not able to account for the effects of ethnicity, together with other potential drivers of disease, in our modelling at the regional level, which might have resulted in partially biased prevalence for each geographical region. Additionally, the lack of assessment of risk factors for carotid stenosis restricted our ability to estimate the regional prevalence of carotid stenosis. A third limitation was that none of the included articles were based on investigations in the Eastern Mediterranean region, so our prevalence estimates for the Eastern Mediterranean region might not precisely reflect the real situation. Therefore, to better explore the distributions of diseases at finer dimensions, scale-up of high-quality data on the epidemiology of carotid atherosclerosis is needed, especially through prospective cross-national studies using comparable definitions and assessments.

We showed that increased carotid intima-media thickness and carotid plaque are common disorders in the general population worldwide. The large number of people living with carotid plaque or carotid stenosis might be indicative of future considerable burden of cardiovascular diseases and is a major public health concern worldwide. Smoking, diabetes, and hypertension are common risk factors for both increased carotid intima-media thickness and carotid plaque. Approximately a third of global cases of increased carotid intima-media thickness and carotid plaque were in the Western Pacific region in 2015. Because of the prominent role of ageing as a risk factor for carotid atherosclerosis, a larger number of people affected by carotid atherosclerosis are expected in the context of global demographic ageing.

Contributors

PS and YZ planned the study and IR and PS designed the methods. PS, YZ, ZF, and HW contributed to the literature review and PS and YZ extracted data. PS, YZ, and IR did the statistical analyses. PS prepared the first draft of the manuscript with important contributions from YC, KR, FGRF, and FJIF. All authors interpreted results, commented on drafts of the manuscript, and approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

All data generated or analysed in this study are included in the appendix.

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