



Cross vascular risk for first and recurrent hospitalised atherothrombosis determined retrospectively from linked data

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Structured Abstract

Objectives – To determine sex and age-specific risk ratios for first-ever and recurrent hospitalisation for cerebrovascular, coronary and peripheral arterial disease in persons with versus without other vascular history in Western Australia from 2005-2007.

Design – Cross-sectional linkage study.

Setting – Hospitalised population in a representative Australian State.

Participants – All persons aged 34 to 85 years between 1 January 2005 and 31 December 2007 hospitalised with a principal diagnosis of atherothrombosis.

Data sources – Person-linked file of statutory collected administrative morbidity and mortality records.

Main outcome measures – Sex and age-specific risk ratios for first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery using a 15-year lead-in to determine prior events.

Results – Over 3 years, 40,877 (66% men; 55% first-ever) were hospitalised for atherothrombosis. For each arterial territory, age-specific recurrent rates were higher than the corresponding first-ever rates, with the biggest difference seen in the youngest age groups. For all types of first-ever atherothrombosis, rates were higher in those with other vascular history and risk ratios declined with advancing age (trend: all $P < 0.0001$) and remained significantly > 1 even for 75-84 year-olds. Whereas, for recurrent events, rates were marginally higher in those with other vascular history and no risk ratio-age trend was apparent with several not significantly > 1 (trend: all $P > 0.13$).

Conclusions - This study of hospitalised atherothrombosis suggests first-events predominate and that the risk of further events in the same or other arterial territory is very high for all ages and both sexes, accentuating the necessity for early and sustained active prevention.

Article focus

- Stroke and heart attack dominate the vascular burden
- Vascular disease rates rise steeply with age
- Cross vascular risk is predictive of disease recurrence

Key messages

- First-ever atherothrombosis leads the vascular burden
- The risk of a new vascular event in same or another territory is universally very high
- Target primary and secondary prevention to reduce the population disease burden

Strengths and limitations of this study

- Quantification of new and recurrent vascular risk by disease subtype and prior history
- Excluding the very elderly, non-hospitalised events and underdiagnoses of other vascular disease likely overestimated the dominance of coronary events
- Including non-acute hospitalisations will have increased the absolute event rates but had negligible effect on relative comparisons.

Introduction

Few studies have reported population-based estimates of the rate and determinants of incident and recurrent vascular events of the brain (cerebrovascular disease), coronary (coronary heart disease) and periphery (peripheral arterial disease) collectively. The Oxford Vascular Study[1] indicated that 63% of all atherothrombosis subtypes were incident (first-ever) events, and 37% recurrent. Cerebrovascular events were most common, more than coronary, and all rates rose steeply with age. In contrast, the international REACH Registry[2] of atherothrombotic disease in primary-care suggested that coronary events were most common, and that history of symptomatic atheroma in more than one vascular bed was a strong predictor of higher rates of recurrence in the same and other vascular beds.

We aimed to explore the application of the results from the OXVASC and REACH studies[1,2] in a population-based study of hospitalisations for vascular disease among Western Australians aged 35-84 years between 2005 and 2007. Our specific aims were to determine: (1) the absolute age and sex-specific annual rates of first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery; (2) the independent, significant contributions of atherothrombosis in a different vascular bed to first-ever and recurrent hospitalisations for symptomatic events of the brain, coronary and periphery.

Methods

Setting and data source

We conducted a cross-sectional data linkage study of statutory collected administrative data with no direct participant contact. The demographic profile and main health indices for WA are reflective of the Australian population.[3] Linked public and private hospital morbidity

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3 and mortality data were extracted retrospectively from the WA Data Linkage System which
4 is regularly audited for quality.[4] Person-based records are linked with >99% accuracy using
5 probabilistic matching on standard criteria.[4] A linked file of all hospital admissions and
6 deaths for all persons experiencing a cardiovascular event from 1 January 1990 to 31
7 December 2007 was available. As morbidity data in the very elderly are considered less
8 reliable, event rates are calculated and reported for people aged 35-84 years.
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Atherothrombosis diagnoses were identified from discharge records according to the International Classification of Disease (ICD) versions 9-Clinical Modification and 10-Australian Modification.[5] The study was approved by research ethics committees at The University of WA (#RA/4/1/1491) and the Department of Health WA (#2009/18).

Definition and classification of atherothrombosis categories

Emergency and elective hospital admissions for brain, coronary and periphery ischaemia were identified from principal diagnoses on the discharge records and are described elsewhere.[6] Briefly, coronary included myocardial infarction, unstable angina, stable angina or other ischaemic heart disease; brain included cerebral infarction, transient ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke or intracerebral haemorrhage; and periphery comprised atherosclerosis of the aorta, renal arteries or arteries of the extremities, unspecified peripheral vascular disease, Buerger's disease or stricture of arteries. Hospital morbidity codes for brain[7], coronary[8] and periphery[9] ischaemia have been previously validated, as have vascular deaths.[10] Hospital transfers were counted as one admission, as were readmissions for the same condition within 28 days for coronary, and within one day for each of brain and periphery episodes.

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3 All atherothrombosis hospitalisations between 1 January 2005 and 31 December 2007 were
4 classified by vascular bed (or disease subtype), and as first-ever or recurrent (or event type).
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6 First-ever events were defined as having no hospitalisation in the same vascular bed during a
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8 15-year look-back period, otherwise the event was classified as recurrent. The same 15-year
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10 look back period was used to determine the binary variable of prior hospitalisation for other
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12 vascular manifestations. The 15-year look-back period was also used to identify the
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14 comorbidities of diabetes, hypertension, chronic kidney disease, atrial fibrillation, heart
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16 failure, chronic lung disease and cancer. There were <0.001% missing values for any of the
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18 variables used in this study.
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27 *Statistical analysis*

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30 Males and females were analysed separately. For each disease subtype, selected differences
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32 in patient characteristics (age by event type, and first-ever events by other vascular history)
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34 were evaluated using t-tests and χ^2 respectively. Overall proportions of first-ever and
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36 recurrent disease patients with hypertension, diabetes, chronic kidney disease, atrial
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38 fibrillation, heart failure, chronic lung disease and cancer were calculated. Age-specific first-
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40 ever and recurrent rates were calculated for each of brain, coronary and periphery stratified
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42 by other vascular history, using the number of events for that disease subtype over the three
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44 years (2005-2007) as the numerator and the corresponding disease-free (prevalent cases
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46 excluded) or disease-specific WA population as the denominator, respectively. Poisson
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48 regression was used to estimate risk ratios for first-ever and recurrent hospitalisations for
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50 each vascular bed for people with other vascular history compared with people without other
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52 vascular history. Models include sex, 5-year age group, and other vascular disease history.
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55 An interaction term of other vascular disease by 10-year age-group was added to the Poisson
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3 model to test for trend in the risk ratio across age groups. Whilst technically we have
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5 estimated rate ratios these are interpreted as 1-year risk ratios as these two ratios are
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7 numerically very similar when the rates have small magnitude. Data analyses were performed
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9 using SAS (version 9.3),[11] and statistical significance was set at $p < 0.05$.
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12 13 14 15 **Results**

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18 There were 27,156 hospitalisations (53% first-ever) for atherothrombosis in men and 13,721
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20 (59% first-ever) in women aged 35 to 84 years between 2005 and 2007 (Table 1). Seventy-six
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22 percent of brain admissions were first-ever, whereas just over half were first-ever for
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24 coronary and periphery. Coronary patients were younger for both first-ever and recurrent
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26 admissions compared with their brain and periphery counterparts. The percentage of cases in
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28 the 75-84 year age group varied from a low of 17% in men for first-ever coronary event, to a
29
30 high of 56% in women for recurrent brain events. Hypertension was the most common
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32 comorbidity followed by diabetes and chronic kidney disease. Periphery patients were less
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34 likely to be admitted acutely and more likely to undergo angiography and/or invasive
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36 intervention than brain or coronary patients.
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44 Coronary admissions dominated first-ever (67% in men and 61% in women) and recurrent
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46 hospitalisations (80% in men and 77% in women) for atherothrombosis (Table 1). Only 6%
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48 of first-ever coronary events in men and women had a prior admission for other vascular
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50 disease, compared with first-ever brain (27% men, 18% women) and first-ever periphery
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52 (44% men, 30% women) hospitalisations. Recurrent events were more likely than first-ever
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54 events to have a history of vascular disease in another vascular bed.
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Atherothrombosis event rates and risk ratios

Figure 1 shows sex and age-specific first-ever and recurrent hospitalisation rates for each disease subtype by history of other vascular disease. Age-specific rates ranged from about 3/1000 for first-ever brain event with no other vascular history to about 200/1000 for recurrent coronary event with other vascular history. For each vascular bed, age-specific recurrent rates in those with and without other vascular history were higher than the first-ever rates, with the biggest difference seen in the youngest age groups. For first-ever atherothrombosis, rates were generally higher in those with other vascular history compared with no other vascular history, particularly in the youngest age groups. There was little difference between those with and without other vascular history for recurrent rates, a trend seen across all age groups, although there were no recurrent hospitalisations for brain or periphery ischaemia involving another vascular territory in the 35-44 year age group in men.

Table 2 shows sex and age-specific risk ratios for first-ever and recurrent hospitalisation by disease subtype comparing persons with other vascular history to those without. The highest risk ratios were for first-ever brain hospitalisations in women 35-44 years (risk ratios 31.5, 95% CI 13.7 to 72.5) and for first-ever periphery event in men and women 35-44 years (risk ratios 21.7, 95% CI 6.3 to 75.1; risk ratios 19.2, 95% CI 2.5 to 145.9, respectively), although confidence intervals were wide. The risk of a first-ever event was greater for those with versus without other vascular history in all age groups, however risk ratios for all first-ever disease subtypes declined with advancing age (trend: all $P < 0.0001$). Risk ratios for recurrent hospitalisations were smaller than for first-ever hospitalisations and several (including all risk ratios for recurrent periphery event) were not significant. Further, risk ratios for recurrent hospitalisations showed no trend with advancing age (trend: all $P > 0.05$).

Discussion

This nationally representative population study of 40,877 first-ever and recurrent hospitalised atherothrombosis documents sex and age-specific risk ratios by vascular bed and history of other vascular disease. The majority of hospitalisations are first-ever, led by coronary, then brain and least for periphery; whilst first-ever rates without a history of other vascular disease rose steeply with age. Recurrent hospitalisation rates in men and women for any disease subtype are substantially higher than the corresponding first-ever rates, although narrowed with advancing age. A history of other vascular disease was associated with a high risk of a new event in another vascular bed in younger men and women. In contrast, a history of other vascular disease had little influence on recurrent events of any type and at any age. Greater sex and age-specific risk ratios occurred in first-ever brain and periphery hospitalisations compared with coronary events. There was less variance in risk ratios for recurrent events across disease subtypes. These findings suggest that once atherothrombosis is clinically manifest in any vascular bed, the risk of further events in the same or another vascular location is very high for all ages and both sexes. This reinforces the need for active secondary prevention in all patients with atherothrombotic disease of any type and regardless of age.

Strengths and limitations

Extensive and high-quality person-based linkage of all hospitalised atherothrombosis by other vascular history enabled determination of first-ever and recurrent rates and disease risk ratios.[4] Events were identified from the principal diagnosis at discharge and in-hospital death code where apparent, as previously validated by our group,[7-10] and others.[12] Sex and age-specific findings are largely consistent within and between disease subtypes, although the risk ratio's with wide CIs in 35-44 age groups should be interpreted with caution. Nonfatal brain/coronary attacks treated in the community were not included in the

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3 analyses but are expected to be small in number.[6] Recognised underdiagnoses of peripheral
4 arterial disease and cerebrovascular events may have resulted,[13] thus diluting their relative
5 contribution to the total hospitalised atherothrombosis burden. Excluding the very elderly has
6 likely overestimated the dominance of coronary events at the expense of brain events, as
7 would the associated elective admissions for the diagnostic (e.g. stress testing, coronary
8 angiography) and coronary revascularisation procedures. The inclusion of non-acute
9 hospitalisations for greater coverage of elective procedures will have increased the absolute
10 rates of events but had negligible effect on relative comparisons.
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24 *Comparisons with other studies*

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27 The age distribution and medical profile of each disease subtype in this representative
28 Australian study are consistent with other hospitalised population studies for myocardial
29 infarction [14,], stroke [15] and peripheral arterial disease.[16] We found little difference in
30 recurrent rates by sex and age, which is entirely consistent with the non-uniform findings of
31 others.[18, 17-20] Differences in methodology likely account for the variability, including:
32 sample size, case definition, all hospitalisations, age restrictions, ethnicity, risk factor profile,
33 duration of follow-up and adjustment for covariates.
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45 The comprehensive population OXVASC study [1] confirms that the majority of
46 atherothrombosis is incident (63% versus 57% in the present study), but led by stroke in that
47 population, and that rates rise steeply with age. The large multinational REACH Registry
48 suggests coronary events dominate the atherothrombosis burden and supports incremental
49 higher rates with other arterial disease involvement.[21] In a separate REACH analysis[13],
50 patients with peripheral disease experienced lower atherothrombosis rates than patients with
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3 stroke or coronary disease, independent of other vascular history. There were no differences
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5 in atherothrombosis rates by gender, possibly due to low enrolment of women in that
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7 study.[22] Two smaller studies, the SIRO trial [23] and MITICO study [24] reported stroke
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9 patients with polyvascular disease had higher rates of recurrence. For co-morbidities, high
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11 proportions of first-ever or recurrent atherothrombosis with hypertension, diabetes and
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13 chronic kidney disease have been variously identified in population and cohort studies.[15,
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20 21 *Implication of results*

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24 These sex and age-specific rates and risk ratios for first-ever and recurrent hospitalised
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26 atherothrombosis by vascular bed and history of other vascular disease permit comparisons of
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28 secondary over primary prevention. To minimize the disease burden on the population and
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30 hospitals we should aim to prevent the 56% first-ever hospitalisations, in particular for the
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32 brain where it is 76%. The prevention of recurrent events is also very important (and not a
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34 mutually exclusive) priority, as they contribute a substantial volume of all hospitalisations,
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36 about 44%. The substantially higher risk ratios for recurrent events in persons with and
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38 without a history of other vascular disease magnify the scope for systematic secondary
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40 prevention across disease subtypes.
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48 In Australia, increased uptake and adherence to antiplatelet, blood pressure-lowering and
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50 lipid-lowering medication in persons with established atherothrombosis, and long-term anti-
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52 smoking campaigns are priority targets for improving cardiovascular outcomes.[28] Two
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54 Australian general practice studies suggest the application of these proven secondary
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56 prevention measures continues to be suboptimal.[29, 30] These findings are poignant given
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3 the high rates of recurrent events and raised risk ratios in men and women across the age span
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5 in the present study. Further, the higher rates of a first-ever admission where there is a history
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7 of vascular disease in a different territory, particularly in the younger age groups, necessitates
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9 more aggressive treatment of risk factors. There was no clear gender difference which may be
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11 because of the similarly high levels of comorbidities in men and women, or because results
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13 were stratified by age, although there may be differences in the over 85 year age group which
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15 we have not investigated. Our findings have potential implications for the management of
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17 approximately 0.25 million (4.3% of the population) women and 0.5 million (8.6%) men in
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19 Australia hospitalised for atherothrombosis.[6]
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27 Contributing to the high risk ratios of recurrent atherothrombosis in both sexes is that over
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29 half are hypertensive and around a quarter variously have diabetes, chronic kidney disease,
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31 atrial fibrillation and heart failure, consistent with other studies.[15, 17, 21, 26] Such
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33 comorbidities will likely complicate clinical treatment during rehospitalisation and
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35 subsequent chronic care.
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42 *Conclusions*

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44 We have shown in a population-based study of hospitalised atherothrombosis that first-ever
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46 events predominate and that once vascular disease clinically manifest, the risk of further
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48 events in the same or another vascular bed is very high, even for the young, supressing the
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50 usual demographic effects. These findings highlight the need for greater awareness among
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52 clinicians, patients and funders as to the level of risk related to recurrent events and detail the
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54 cross-risk associated with a prior hospitalisation in other vascular locations. These findings
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3 have important implications for prevention strategies, and the prioritising of resources for
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5 service provision and research, and they signal an upward trajectory in absolute numbers of
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7 events as the population ages. Data on hospital incidence, recurrence, and event risk ratios
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9 across the vasculature will also permit modelling the effect of shared secondary preventive
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11 treatments, such as cardioprotective pharmacotherapy and lifestyle changes, on the total
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13 burden of hospitalised atherothrombosis.
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Declaration of Conflicting Interests

None Declared

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Contributors

TB, MK, GJH PEN and JH conceived and designed the study; LN, FS, SH, TB prepared the data files for analysis; TB, LN undertook the data analysis and drafted the paper; MK wrote the statistical plan and together with AB provided advanced statistical support; JH, GJH, PEN, PLT, FS provided clinical advice; all authors contributed to interpretation of data, reviewing article drafts, and approving the final manuscript. TB is guarantor.

Data sharing

The sharing of the linked data file is not permitted under the conditions under which ethics for the study was granted

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5 Figure 1 A-F. Age-specific rates for hospitalised coronary, brain and periphery ischaemia by
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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p 1, 3 p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5
Objectives	3	State specific objectives, including any prespecified hypotheses	p 5
Methods			
Study design	4	Present key elements of study design early in the paper	p 5.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 5.6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	p 5-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 6.7
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	p 6.7
Bias	9	Describe any efforts to address potential sources of bias	p 6, 10, 1
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7.8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	p 7.8 p 7
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	p 8, Table 1 N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Figure 1
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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	

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Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

p 9

p 10,11

p 11,12

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p 15

*Give information separately for exposed and unexposed groups.

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.

Table 1. Characteristics of atherothrombosis hospitalisations[†] 2005-2007, Western Australia

DISEASE SUBTYPE <i>cells in %, unless otherwise specified</i>	MEN		WOMEN	
	First-ever	Recurrent	First-ever	Recurrent
Coronary event, n=29,048 (row %)	9682 (33)	10105 (35)	4970 (17)	4291 (15)
Mean age [□] , (SD) years	62.2 (11.4)	66.3 (10.8)	66.0 (11.8)	69.7 (10.7)
Patients aged 75-84/35-54 years	17.2/26.0	26.9/15.5	29.2/18.9	40.9/10.7
Prior cerebrovascular disease	3.4	7.9	3.8	8.3
Prior peripheral arterial disease	1.9	4.7	1.7	4.2
Diabetes	20.7	33.7	23.9	39.7
Hypertension	50.7	78.1	59.9	85.4
Chronic Kidney Disease	7.7	18.5	9.3	20.8
Atrial Fibrillation	11.1	22.1	12.2	21.3
Heart Failure	8.9	20.7	12.3	27.1
Chronic Lung Disease	5.2	13.4	8.2	19.7
Cancer	8.2	13.9	9.9	17.5
Acute Admission [†]	51.2	36.9	52.1	42.7
Brain event, n=7862 (row %)	3556 (45)	1149 (15)	2465 (31)	692 (9)
Mean age [□] , (SD) years	68.3 (11.0)	71.2 (9.9)	70.6 (11.6)	72.7 (10.7)
Patients aged 75-84/35-54 years	36.1/12.9	47.2/8.0	48.7/12.2	56.1/7.5
Prior coronary heart disease	20.6	27.0	15.0 ^f	22.4
Prior peripheral arterial disease	2.2	5.1	2.1	2.6
Diabetes	26.9	33.9	26.0	33.1

Hypertension	65.9	81.3	66.9	81.8
Chronic Kidney Disease	12.1	17.8	11.5	21.5
Atrial Fibrillation	20.3	26.0	21.3	33.5
Heart Failure	9.8	14.5	12.0	21.0
Chronic Lung Disease	8.3	14.5	10.2	15.3
Cancer	14.6	18.5	14.3	18.4
Acute Admission†	73.8	60.8	76.5	70.5
Periphery event, n=3967 (row %)	1276 (32)	1388 (35)	680 (17)	623 (16)
Mean age [□] , (SD) years	69.3 (10.1)	70.5 (9.6)	71.2 (11.0)	72.7 (10.0)
Patients aged 75-84/35-54 years	36.9/8.9	40.3/6.4	48.5/10.3	54.6/7.2
Prior coronary heart disease	27.5	30.4	18.1 ^f	24.4
Prior cerebrovascular disease	6.4	8.1	6.3	8.0
Diabetes	11.5	8.6	11.5	7.5
Hypertension	47.7	56.8	52.5	64.0
Chronic Kidney Disease	14.4	16.7	12.8	14.3
Atrial Fibrillation	16.3	14.7	14.7	17.5
Heart Failure	13.2	13.0	11.0	17.2
Chronic Lung Disease	11.4	16.4	11.3	14.4
Cancer	12.6	16.4	11.6	14.1
Acute Admission†	12.2	13.0	14.6	11.4
All vascular events, n (40,877) (row-%)	14,514 (35)	12,642 (31)	8115 (20)	5606 (14)

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3 † For coronary disease, cerebral infarction or transient ischaemic attack, or atherosclerosis of
4
5 the periphery.

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7 □ For each disease subtype, mean age varied by sex and event type (incident versus recurrent)
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9 (All $P < 0.0001$).

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12 ^f For first-ever brain and periphery events, proportions with prior coronary disease varied by
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14 sex (both $P < 0.0001$);

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17 SD=standard deviation
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Table 2. Hospitalised atherothrombotic disease one-year risk ratios by sex and age-group comparing persons with other vascular history to those without: Western Australia 2005-2007

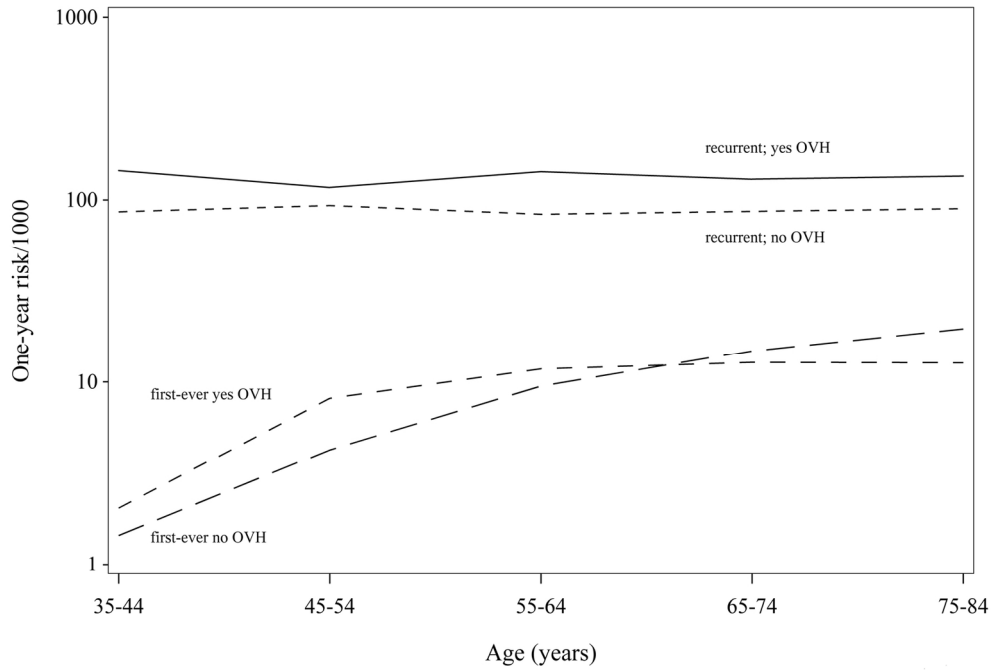
Age-group years		Hospitalised disease one-year risk ratio (95% confidence intervals)					Age group
		35-44	45-54	55-64	65-74	75-84	trend p value
M E N	Coronary event first-ever	2.5 (0.8 to 7.9)	3.5 (2.5 to 4.9)	2.3 (1.9 to 2.8)	1.6 (1.4 to 1.9)	1.2 (1.1 to 1.4)	<0.0001
	recurrent	1.6 (0.8 to 3.3)	1.3 (0.9 to 1.7)	1.7 (1.5 to 1.9)	1.5 (1.4 to 1.7)	1.5 (1.4 to 1.6)	0.6283
	Brain event first-ever	5.4 (2.2 to 13.3)	5.0 (3.7 to 6.7)	2.2 (1.8 to 2.7)	1.6 (1.4 to 1.8)	1.2 (1.1 to 1.4)	<0.0001
	recurrent	—*	1.7 (1.0 to 2.9)	1.3 (0.9 to 1.9)	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)	0.4721
	Periphery event first-ever	21.7 (6.3 to 75.1)	5.1 (3.0 to 8.8)	4.9 (3.8 to 6.3)	2.8 (2.3 to 3.4)	1.7 (1.4 to 2.1)	<0.0001
	recurrent	—*	0.7 (0.4 to 1.3)	1.1 (0.8 to 1.4)	0.8 (0.7 to 1.0)	0.9 (0.7 to 1.0)	0.9696
W O M E	Coronary event first-ever	5.6 (1.4 to 22.5)	5.3 (3.0 to 9.1)	3.0 (2.1 to 4.3)	2.2 (1.8 to 2.8)	1.7 (1.5 to 2.0)	<0.0001
	recurrent	1.9 (0.9 to 4.1)	1.4 (0.9 to 2.1)	2.3 (1.8 to 2.9)	1.4 (1.2 to 1.7)	1.5 (1.3 to 1.7)	0.1357
	Brain event first-ever	31.5 (13.7 to 72.5)	7.4 (4.4 to 12.3)	3.0 (2.1 to 4.4)	2.4 (1.9 to 2.9)	1.7 (1.5 to 1.9)	<0.0001
	recurrent	1.9 (0.4 to 8.0)	1.0 (0.3 to 3.3)	1.3 (0.7 to 2.3)	1.4 (1.0 to 2.0)	1.3 (1.0 to 1.6)	0.8530
	Periphery event first-ever	19.2 (2.5 to 145.9)	11.1 (5.0 to 24.7)	6.7 (4.1 to 11.1)	3.7 (2.7 to 5.1)	2.0 (1.6 to 2.5)	<0.0001

N	recurrent	1.7 (0.2 to 13.7)	1.1 (0.5 to 2.4)	0.6 (0.4 to 1.2)	1.1 (0.8 to 1.5)	0.9 (0.7 to 1.1)	0.8577
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*No events in these age-groups.

For peer review only

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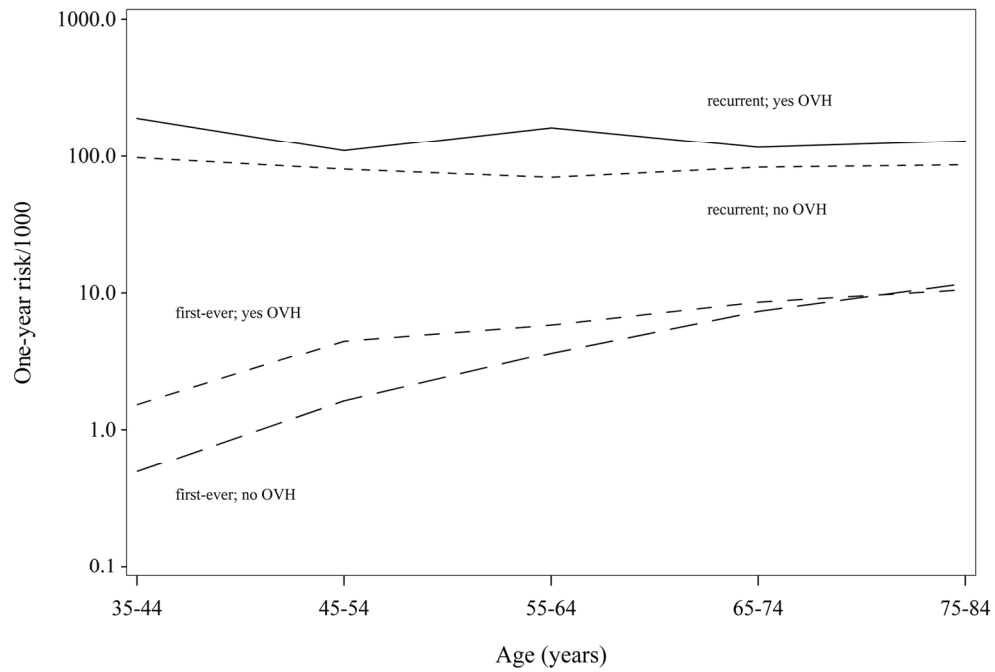


Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in men
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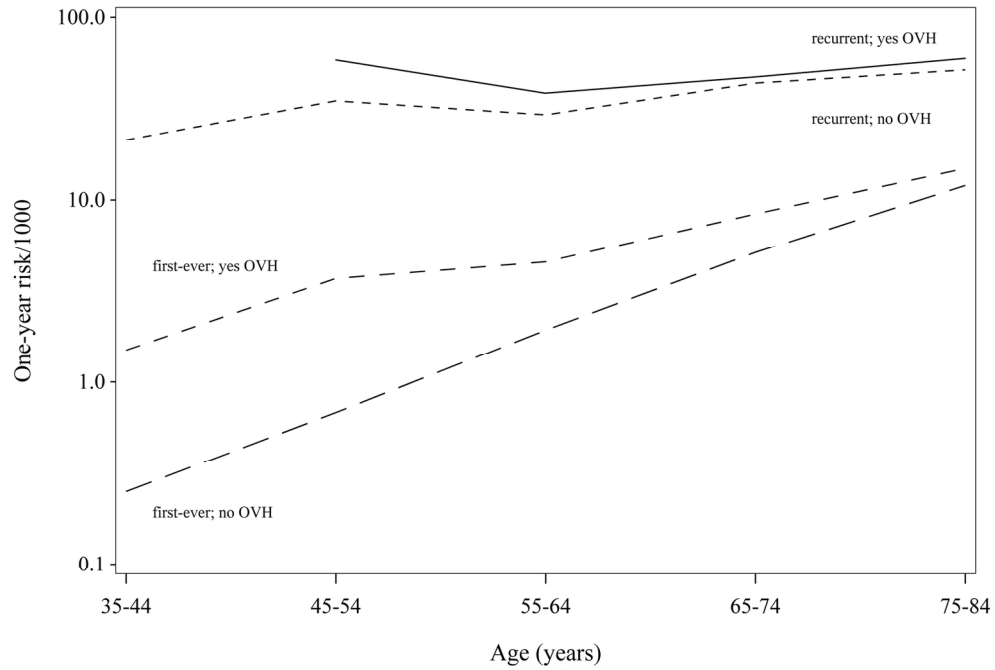
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Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in women
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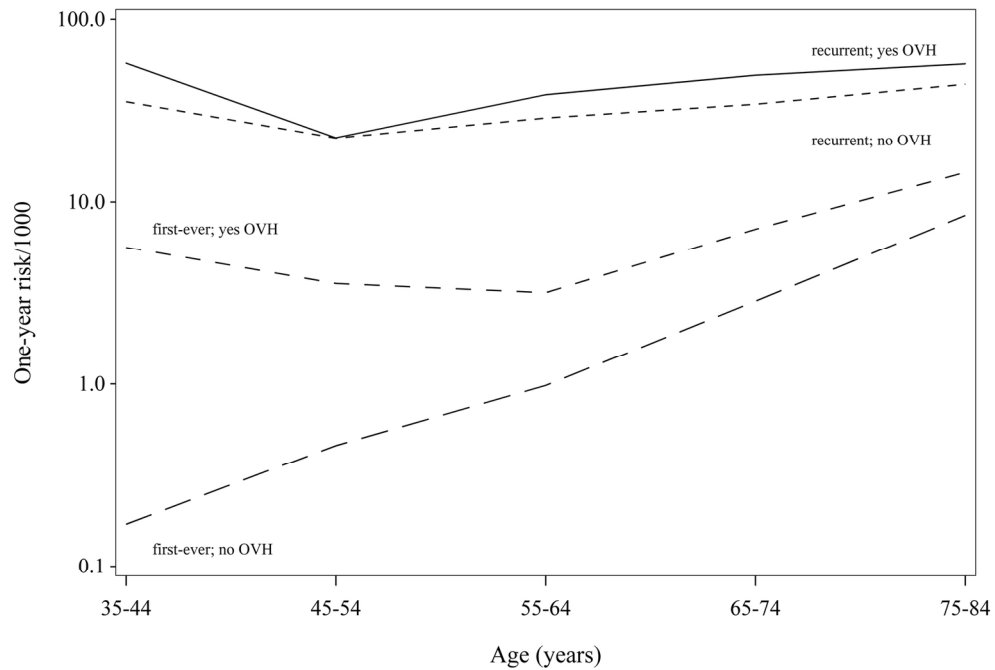


Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in men
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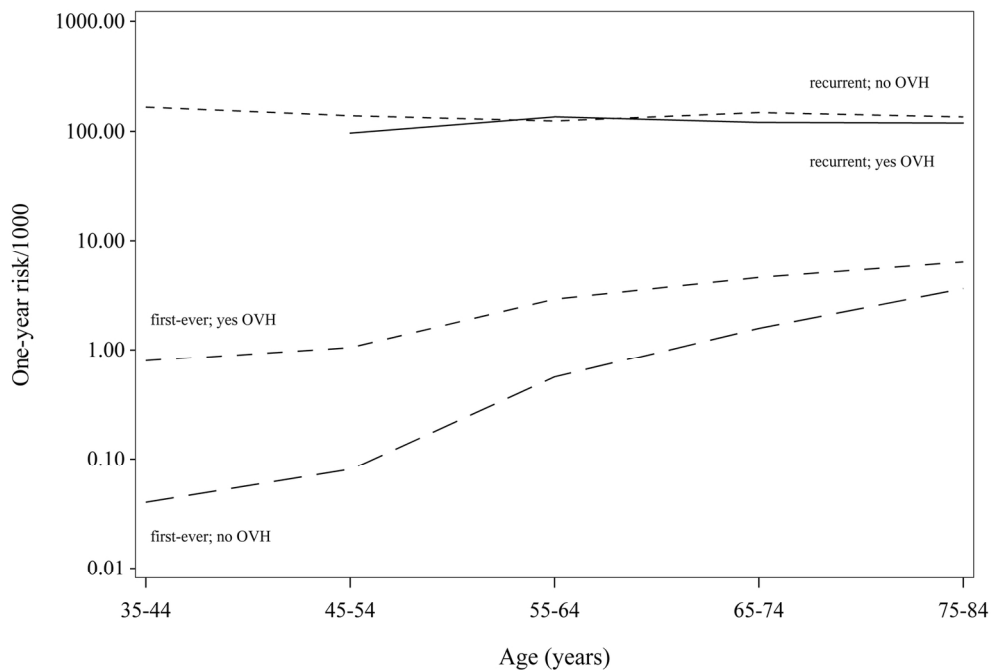
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Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in women
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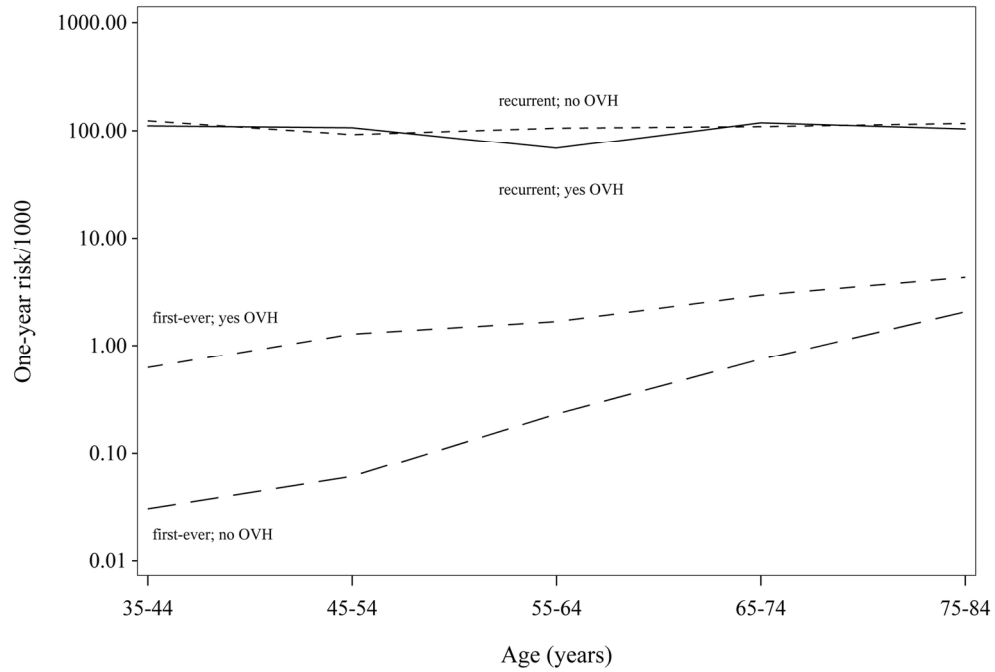


Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in men
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Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in women
76x57mm (600 x 600 DPI)

Review only



**Cross vascular risk for first and recurrent hospitalised
atherothrombosis determined retrospectively from linked
data**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003813.R1
Article Type:	Research
Date Submitted by the Author:	21-Oct-2013
Complete List of Authors:	Briffa, Thomas; University of Western Australia, School of Population Health Nedkoff, Lee; The University of Western Australia, School of Population health Knuiman, Matthew; The University of Western Australia, School of Population Health Hankey, Graeme; The University of Western Australia, School of Medicine and Pharmacology Norman, Paul; The University of Western Australia, School of Surgery Hung, Joseph; The University of Western Australia, School of Medicine and Pharmacology; Sir Charles Gairdner Hospital Unit, Cardiovascular Medicine Thompson, Peter; Sir Charles Gairdner Hospital Unit, Cardiovascular Medicine Hickling, Siobhan; The University of Western Australia, School of Population Health Bremner, Alexandra; The University of Western Australia, School of Population Health Sanfilippo, Frank; The University of Western Australia, School of Population Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Health policy
Keywords:	Cardiac Epidemiology < CARDIOLOGY, VASCULAR MEDICINE, PREVENTIVE MEDICINE

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Manuscripts

1
2 **Title:** Cross vascular risk for first and recurrent hospitalised atherothrombosis determined
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4 retrospectively from linked data
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10 **Short Title:** Cross vascular disease risk
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16 **First Author:** TG Briffa, Research Associate Professor, School of Population Health
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Word Count: Abstract: 250; Body of text: 2481

Subject Codes: [8] Epidemiology [100] Health Policy and Outcome Research

Structured Abstract

Objectives – To determine sex and age-specific risk ratios for first-ever and recurrent hospitalisation for cerebrovascular, coronary and peripheral arterial disease in persons with versus without other vascular history in Western Australia from 2005-2007.

Design – Cross-sectional linkage study.

Setting – Hospitalised population in a representative Australian State.

Participants – All persons aged 34 to 85 years between 1 January 2005 and 31 December 2007 hospitalised with a principal diagnosis of atherothrombosis.

Data sources – Person-linked file of statutory collected administrative morbidity and mortality records.

Main outcome measures – Sex and age-specific risk ratios for first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery using a 15-year lead-in to determine prior events.

Results – Over 3 years, 40,877 (66% men; 55% first-ever) were hospitalised for atherothrombosis. For each arterial territory, age-specific recurrent rates were higher than the corresponding first-ever rates, with the biggest difference seen in the youngest age groups. For all types of first-ever atherothrombosis, rates were higher in those with other vascular history and risk ratios declined with advancing age (trend: all $P < 0.0001$) and remained significantly > 1 even for 75-84 year-olds. Whereas, for recurrent events, rates were marginally higher in those with other vascular history and no risk ratio-age trend was apparent with several not significantly > 1 (trend: all $P > 0.13$).

Conclusions - This study of hospitalised atherothrombosis suggests first-events predominate and that the risk of further events in the same or other arterial territory is very high for all ages and both sexes, accentuating the necessity for early and sustained active prevention.

Article focus

- Stroke and heart attack dominate the vascular burden
- Vascular disease rates rise steeply with age
- Cross vascular risk is predictive of disease recurrence

Key messages

- First-ever atherothrombosis leads the vascular burden
- The risk of a new vascular event in same or another territory is universally very high
- Target primary and secondary prevention to reduce the population disease burden

Strengths and limitations of this study

- Quantification of new and recurrent vascular risk by disease subtype and prior history
- Excluding the very elderly, non-hospitalised events and underdiagnoses of other vascular disease likely overestimated the dominance of coronary events
- Including non-acute hospitalisations will have increased the absolute event rates but had negligible effect on relative comparisons.

Introduction

Few studies have reported population-based estimates of the rate and determinants of incident and recurrent vascular events of the brain (cerebrovascular disease), coronary (coronary heart disease) and periphery (peripheral arterial disease) collectively. The Oxford Vascular Study[1] indicated that 63% of all atherothrombosis subtypes were incident (first-ever) events, and 37% recurrent. Cerebrovascular events were most common, more than coronary, and all rates rose steeply with age. In contrast, the international REACH Registry[2] of atherothrombotic disease in primary-care suggested that coronary events were most common, and that history of symptomatic atheroma in more than one vascular bed was a strong predictor of higher rates of recurrence in the same and other vascular beds.

We aimed to explore the application of the results from the OXVASC and REACH studies[1,2] in a population-based study of hospitalisations for vascular disease among Western Australians aged 35-84 years between 2005 and 2007. Our specific aims were to determine: (1) the absolute age and sex-specific annual rates of first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery; (2) the independent, significant contributions of atherothrombosis in a different vascular bed to first-ever and recurrent hospitalisations for symptomatic events of the brain, coronary and periphery.

Methods

Setting and data source

We conducted a cross-sectional data linkage study of statutory collected administrative data with no direct participant contact. The demographic profile and main health indices for WA are reflective of the Australian population.[3] Linked public and private hospital morbidity

1
2 and mortality data were extracted retrospectively from the WA Data Linkage System which
3 is regularly audited for quality.[4] Person-based records are linked with >99% accuracy using
4 probabilistic matching on standard criteria.[4] A linked file of all hospital admissions and
5 deaths for all persons experiencing a cardiovascular event from 1 January 1990 to 31
6 December 2007 was available. As morbidity data in the very elderly are considered less
7 reliable, event rates are calculated and reported for people aged 35-84 years.

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Atherothrombosis diagnoses were identified from discharge records according to the
International Classification of Disease (ICD) versions 9-Clinical Modification and 10-
Australian Modification.[5] The study was approved by research ethics committees at The
University of WA (#RA/4/1/1491) and the Department of Health WA (#2009/18).

Definition and classification of atherothrombosis categories

Emergency and elective hospital admissions for brain, coronary and periphery ischaemia
were identified from principal diagnoses on the discharge records and are described
elsewhere.[6] Briefly, coronary included myocardial infarction, unstable angina, stable
angina or other ischaemic heart disease; brain included cerebral infarction, transient
ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke
or intracerebral haemorrhage; and periphery comprised atherosclerosis of the aorta, renal
arteries or arteries of the extremities, unspecified peripheral vascular disease, Buerger's
disease or stricture of arteries. Hospital morbidity codes for brain[7], coronary[8] and
periphery[9] ischaemia have been previously validated, as have vascular deaths.[10] Hospital
transfers were counted as one admission, as were readmissions for the same condition within
28 days for coronary, and within one day for each of brain and periphery episodes.

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2 All atherothrombosis hospitalisations between 1 January 2005 and 31 December 2007 were
3 classified by vascular bed (or disease subtype), and as first-ever or recurrent (or event type).
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5 First-ever events were defined as having no hospitalisation in the same vascular bed during a
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7 15-year look-back period, otherwise the event was classified as recurrent. The same 15-year
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9 look back period was used to determine the binary variable of prior hospitalisation for other
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11 vascular manifestations. The 15-year look-back period was also used to identify the
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13 comorbidities of diabetes, hypertension, chronic kidney disease, atrial fibrillation, heart
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15 failure, chronic lung disease and cancer. There were <0.001% missing values for any of the
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17 variables used in this study.
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26 *Statistical analysis*

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29 Males and females were analysed separately. For each disease subtype, selected differences
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31 in patient characteristics (age by event type, and first-ever events by other vascular history)
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33 were evaluated using t-tests and χ^2 respectively. Overall proportions of first-ever and
34
35 recurrent disease patients with hypertension, diabetes, chronic kidney disease, atrial
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37 fibrillation, heart failure, chronic lung disease and cancer were calculated. Age-specific first-
38
39 ever and recurrent rates were calculated for each of brain, coronary and periphery stratified
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41 by other vascular history, using the number of events for that disease subtype over the three
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43 years (2005-2007) as the numerator and the corresponding disease-free (prevalent cases
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45 excluded) or disease-specific WA population as the denominator, respectively. Poisson
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47 regression was used to estimate risk ratios for first-ever and recurrent hospitalisations for
48
49 each vascular bed for people with other vascular history compared with people without other
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51 vascular history. Models include sex, 5-year age group, and other vascular disease history.
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55 An interaction term of other vascular disease by 10-year age-group was added to the Poisson
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2 model to test for trend in the risk ratio across age groups. Whilst technically we have
3
4 estimated rate ratios these are interpreted as 1-year risk ratios as these two ratios are
5
6 numerically very similar when the rates have small magnitude. Data analyses were performed
7
8 using SAS (version 9.3),[11] and statistical significance was set at $p < 0.05$.
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11 12 13 **Results**

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17 There were 27,156 hospitalisations (53% first-ever) for atherothrombosis in men and 13,721
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19 (59% first-ever) in women aged 35 to 84 years between 2005 and 2007 (Table 1). Seventy-six
20
21 percent of brain admissions were first-ever, whereas just over half were first-ever for
22
23 coronary and periphery. Coronary patients were younger for both first-ever and recurrent
24
25 admissions compared with their brain and periphery counterparts. The percentage of cases in
26
27 the 75-84 year age group varied from a low of 17% in men for first-ever coronary event, to a
28
29 high of 56% in women for recurrent brain events. Hypertension was the most common
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31 comorbidity followed by diabetes and chronic kidney disease. Periphery patients were less
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33 likely to be admitted acutely and more likely to undergo angiography and/or invasive
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35 intervention than brain or coronary patients.
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44 Coronary admissions dominated first-ever (67% in men and 61% in women) and recurrent
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46 hospitalisations (80% in men and 77% in women) for atherothrombosis (Table 1). Only 6%
47
48 of first-ever coronary events in men and women had a prior admission for other vascular
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50 disease, compared with first-ever brain (27% men, 18% women) and first-ever periphery
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52 (44% men, 30% women) hospitalisations. Recurrent events were more likely than first-ever
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54 events to have a history of vascular disease in another vascular bed.
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57 *Atherothrombosis event rates and risk ratios*
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2 Figure 1 shows sex and age-specific first-ever and recurrent hospitalisation rates for each
3 disease subtype by history of other vascular disease. Age-specific rates ranged from about
4 3/1000 for first-ever brain event with no other vascular history to about 200/1000 for
5 recurrent coronary event with other vascular history. For each vascular bed, age-specific
6 recurrent rates in those with and without other vascular history were higher than the first-ever
7 rates, with the biggest difference seen in the youngest age groups. For first-ever
8 atherothrombosis, rates were generally higher in those with other vascular history compared
9 with no other vascular history, particularly in the youngest age groups. There was little
10 difference between those with and without other vascular history for recurrent rates, a trend
11 seen across all age groups, although there were no recurrent hospitalisations for brain or
12 periphery ischaemia involving another vascular territory in the 35-44 year age group in men.
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29 Table 2 shows sex and age-specific risk ratios for first-ever and recurrent hospitalisation by
30 disease subtype comparing persons with other vascular history to those without. The highest
31 risk ratios were for first-ever brain hospitalisations in women 35-44 years (risk ratios 31.5,
32 95% CI 13.7 to 72.5) and for first-ever periphery event in men and women 35-44 years (risk
33 ratios 21.7, 95% CI 6.3 to 75.1; risk ratios 19.2, 95% CI 2.5 to 145.9, respectively), although
34 confidence intervals were wide. The risk of a first-ever event was greater for those with
35 versus without other vascular history in all age groups, however risk ratios for all first-ever
36 disease subtypes declined with advancing age (trend: all $P < 0.0001$). Risk ratios for recurrent
37 hospitalisations were smaller than for first-ever hospitalisations and several (including all risk
38 ratios for recurrent periphery event) were not significant. Further, risk ratios for recurrent
39 hospitalisations showed no trend with advancing age (trend: all $P > 0.05$).
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55 Discussion

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2 This nationally representative population study of 40,877 first-ever and recurrent hospitalised
3 atherothrombosis documents sex and age-specific risk ratios by vascular bed and history of
4 other vascular disease. The majority of hospitalisations are first-ever, led by coronary, then
5 brain and least for periphery; whilst first-ever rates without a history of other vascular disease
6 rose steeply with age. Recurrent hospitalisation rates in men and women for any disease
7 subtype are substantially higher than the corresponding first-ever rates, although narrowed
8 with advancing age. A history of other vascular disease was associated with a high risk of a
9 new event in another vascular bed in younger men and women. In contrast, a history of other
10 vascular disease had little influence on recurrent events of any type and at any age. Greater
11 sex and age-specific risk ratios occurred in first-ever brain and periphery hospitalisations
12 compared with coronary events. There was less variance in risk ratios for recurrent events
13 across disease subtypes. These findings suggest that once atherothrombosis is clinically
14 manifest in any vascular bed, the risk of further events in the same or another vascular
15 location is very high for all ages and both sexes. This reinforces the need for active secondary
16 prevention in all patients with atherothrombotic disease of any type and regardless of age.
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38 *Strengths and limitations*

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40 Extensive and high-quality person-based linkage of all hospitalised atherothrombosis by other
41 vascular history enabled determination of first-ever and recurrent rates and disease risk
42 ratios.[4] Events were identified from the principal diagnosis at discharge and in-hospital
43 death code where apparent, as previously validated by our group,[7-10] and others.[12] Sex
44 and age-specific findings are largely consistent within and between disease subtypes,
45 although the risk ratio's with wide CIs in 35-44 age groups should be interpreted with
46 caution. Nonfatal brain/coronary attacks treated in the community were not included in the
47 analyses but are expected to be small in number.[6] Recognised underdiagnoses of peripheral
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2 arterial disease and cerebrovascular events may have resulted,[13] thus diluting their relative
3 contribution to the total hospitalised atherothrombosis burden. Excluding the very elderly has
4 likely overestimated the dominance of coronary events at the expense of brain events, as
5 would the associated elective admissions for the diagnostic (e.g. stress testing, coronary
6 angiography) and coronary revascularisation procedures. The inclusion of non-acute
7 hospitalisations for greater coverage of elective procedures will have increased the absolute
8 rates of events but had negligible effect on relative comparisons.
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22 *Comparisons with other studies*

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24 The age distribution and medical profile of each disease subtype in this representative
25 Australian study are consistent with other hospitalised population studies for myocardial
26 infarction [14,], stroke [15] and peripheral arterial disease.[16] We found little difference in
27 recurrent rates by sex and age, which is entirely consistent with the non-uniform findings of
28 others.[18, 17-20] Differences in methodology likely account for the variability, including:
29 sample size, case definition, all hospitalisations, age restrictions, ethnicity, risk factor profile,
30 duration of follow-up and adjustment for covariates.
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42 The comprehensive population OXVASC study [1] confirms that the majority of
43 atherothrombosis is incident (63% versus 57% in the present study), but led by stroke in that
44 population, and that rates rise steeply with age. The large multinational REACH Registry
45 suggests coronary events dominate the atherothrombosis burden and supports incremental
46 higher rates with other arterial disease involvement.[21] In a separate REACH analysis[13],
47 patients with peripheral disease experienced lower atherothrombosis rates than patients with
48 stroke or coronary disease, independent of other vascular history. There were no differences
49 in atherothrombosis rates by gender, possibly due to low enrolment of women in that
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2 study.[22] Two smaller studies, the SIRO trial [23] and MITICO study [24] reported stroke
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4 patients with polyvascular disease had higher rates of recurrence. For co-morbidities, high
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6 proportions of first-ever or recurrent atherothrombosis with hypertension, diabetes and
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8 chronic kidney disease have been variously identified in population and cohort studies.[15,
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10 21, 24-27]
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13 14 15 *Implication of results* 16

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18 These sex and age-specific rates and risk ratios for first-ever and recurrent hospitalised
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20 atherothrombosis by vascular bed and history of other vascular disease permit comparisons of
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22 secondary over primary prevention. To minimize the disease burden on the population and
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24 hospitals we should aim to prevent the 56% first-ever hospitalisations, in particular for the
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26 brain where it is 76%. The prevention of recurrent events is also very important (and not a
27
28 mutually exclusive) priority, as they contribute a substantial volume of all hospitalisations,
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30 about 44%. The substantially higher risk ratios for recurrent events in persons with and
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32 without a history of other vascular disease magnify the scope for systematic secondary
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34 prevention across disease subtypes.
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43 In Australia, increased uptake and adherence to antiplatelet, blood pressure-lowering and
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45 lipid-lowering medication in persons with established atherothrombosis, and long-term anti-
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47 smoking campaigns are priority targets for improving cardiovascular outcomes.[28] Two
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49 Australian general practice studies suggest the application of these proven secondary
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51 prevention measures continues to be suboptimal.[29, 30] These findings are poignant given
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53 the high rates of recurrent events and raised risk ratios in men and women across the age span
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55 in the present study. Further, the higher rates of a first-ever admission where there is a history
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57 of vascular disease in a different territory, particularly in the younger age groups, necessitates
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2 more aggressive treatment of risk factors. There was no clear gender difference which may be
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4 because of the similarly high levels of comorbidities in men and women, or because results
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6 were stratified by age, although there may be differences in the over 85 year age group which
7
8 we have not investigated. Our findings have potential implications for the management of
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10 approximately 0.25 million (4.3% of the population) women and 0.5 million (8.6%) men in
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12 Australia hospitalised for atherothrombosis.[6]
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19 Contributing to the high risk ratios of recurrent atherothrombosis in both sexes is that over
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21 half are hypertensive and around a quarter variously have diabetes, chronic kidney disease,
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23 atrial fibrillation and heart failure, consistent with other studies.[15, 17, 21, 26] Such
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25 comorbidities will likely complicate clinical treatment during rehospitalisation and
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27 subsequent chronic care.
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30 31 32 33 34 *Conclusions*

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37 We have shown in a population-based study of hospitalised atherothrombosis that first-ever
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39 events predominate and that once vascular disease clinically manifest, the risk of further
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41 events in the same or another vascular bed is very high, even for the young, supressing the
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43 usual demographic effects. These findings highlight the need for greater awareness among
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45 clinicians, patients and funders as to the level of risk related to recurrent events and detail the
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47 cross-risk associated with a prior hospitalisation in other vascular locations. These findings
48
49 have important implications for prevention strategies, and the prioritising of resources for
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51 service provision and research, and they signal an upward trajectory in absolute numbers of
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53 events as the population ages. Data on hospital incidence, recurrence, and event risk ratios
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55 across the vasculature will also permit modelling the effect of shared secondary preventive
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2 treatments, such as cardioprotective pharmacotherapy and lifestyle changes, on the total
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4 burden of hospitalised atherothrombosis.
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Declaration of Conflicting Interests

None Declared

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Contributors

TB, MK, GJH PEN and JH conceived and designed the study; LN, FS, SH, TB prepared the data files for analysis; TB, LN undertook the data analysis and drafted the paper; MK wrote the statistical plan and together with AB provided advanced statistical support; JH, GJH, PEN, PLT, FS provided clinical advice; all authors contributed to interpretation of data, reviewing article drafts, and approving the final manuscript. TB is guarantor.

Data sharing

The sharing of the linked data file is not permitted under the conditions under which ethics for the study was granted.

Table 1. Characteristics of atherothrombosis hospitalisations[†] 2005-2007, Western Australia

DISEASE SUBTYPE <i>cells in %, unless otherwise specified</i>	MEN		WOMEN	
	First-ever	Recurrent	First-ever	Recurrent
Coronary event, n=29,048 (row %)	9682 (33)	10105 (35)	4970 (17)	4291 (15)
Mean age [□] , (SD) years	62.2 (11.4)	66.3 (10.8)	66.0 (11.8)	69.7 (10.7)
Patients aged 75-84/35-54 years	17.2/26.0	26.9/15.5	29.2/18.9	40.9/10.7
Prior cerebrovascular disease	3.4	7.9	3.8	8.3
Prior peripheral arterial disease	1.9	4.7	1.7	4.2
Diabetes	20.7	33.7	23.9	39.7
Hypertension	50.7	78.1	59.9	85.4
Chronic Kidney Disease	7.7	18.5	9.3	20.8
Atrial Fibrillation	11.1	22.1	12.2	21.3
Heart Failure	8.9	20.7	12.3	27.1
Chronic Lung Disease	5.2	13.4	8.2	19.7
Cancer	8.2	13.9	9.9	17.5
Acute Admission [†]	51.2	36.9	52.1	42.7
Brain event, n=7862 (row %)	3556 (45)	1149 (15)	2465 (31)	692 (9)
Mean age [□] , (SD) years	68.3 (11.0)	71.2 (9.9)	70.6 (11.6)	72.7 (10.7)
Patients aged 75-84/35-54 years	36.1/12.9	47.2/8.0	48.7/12.2	56.1/7.5
Prior coronary heart disease	20.6	27.0	15.0 ^f	22.4
Prior peripheral arterial disease	2.2	5.1	2.1	2.6
Diabetes	26.9	33.9	26.0	33.1

Hypertension	65.9	81.3	66.9	81.8
Chronic Kidney Disease	12.1	17.8	11.5	21.5
Atrial Fibrillation	20.3	26.0	21.3	33.5
Heart Failure	9.8	14.5	12.0	21.0
Chronic Lung Disease	8.3	14.5	10.2	15.3
Cancer	14.6	18.5	14.3	18.4
Acute Admission†	73.8	60.8	76.5	70.5
Periphery event, n=3967 (row %)	1276 (32)	1388 (35)	680 (17)	623 (16)
Mean age [□] , (SD) years	69.3 (10.1)	70.5 (9.6)	71.2 (11.0)	72.7 (10.0)
Patients aged 75-84/35-54 years	36.9/8.9	40.3/6.4	48.5/10.3	54.6/7.2
Prior coronary heart disease	27.5	30.4	18.1 ^f	24.4
Prior cerebrovascular disease	6.4	8.1	6.3	8.0
Diabetes	11.5	8.6	11.5	7.5
Hypertension	47.7	56.8	52.5	64.0
Chronic Kidney Disease	14.4	16.7	12.8	14.3
Atrial Fibrillation	16.3	14.7	14.7	17.5
Heart Failure	13.2	13.0	11.0	17.2
Chronic Lung Disease	11.4	16.4	11.3	14.4
Cancer	12.6	16.4	11.6	14.1
Acute Admission†	12.2	13.0	14.6	11.4
All vascular events, n (40,877) (row-%)	14,514 (35)	12,642 (31)	8115 (20)	5606 (14)

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2 † For coronary disease, cerebral infarction or transient ischaemic attack, or atherosclerosis of
3
4 the periphery.
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6 □ For each disease subtype, mean age varied by sex and event type (incident versus recurrent)
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9 (All $P < 0.0001$).
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11 ^f For first-ever brain and periphery events, proportions with prior coronary disease varied by
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13 sex (both $P < 0.0001$);
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15 SD=standard deviation
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Table 2. Hospitalised atherothrombotic disease one-year risk ratios by sex and age-group comparing persons with other vascular history to those without: Western Australia 2005-2007

Age-group years		Hospitalised disease one-year risk ratio (95% confidence intervals)					Age group
		35-44	45-54	55-64	65-74	75-84	trend p value
M	Coronary event first-ever	2.5 (0.8 to 7.9)	3.5 (2.5 to 4.9)	2.3 (1.9 to 2.8)	1.6 (1.4 to 1.9)	1.2 (1.1 to 1.4)	<0.0001
	recurrent	1.6 (0.8 to 3.3)	1.3 (0.9 to 1.7)	1.7 (1.5 to 1.9)	1.5 (1.4 to 1.7)	1.5 (1.4 to 1.6)	0.6283
E	Brain event first-ever	5.4 (2.2 to 13.3)	5.0 (3.7 to 6.7)	2.2 (1.8 to 2.7)	1.6 (1.4 to 1.8)	1.2 (1.1 to 1.4)	<0.0001
	recurrent	—*	1.7 (1.0 to 2.9)	1.3 (0.9 to 1.9)	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)	0.4721
N	Periphery event first-ever	21.7 (6.3 to 75.1)	5.1 (3.0 to 8.8)	4.9 (3.8 to 6.3)	2.8 (2.3 to 3.4)	1.7 (1.4 to 2.1)	<0.0001
	recurrent	—*	0.7 (0.4 to 1.3)	1.1 (0.8 to 1.4)	0.8 (0.7 to 1.0)	0.9 (0.7 to 1.0)	0.9696
W	Coronary event first-ever	5.6 (1.4 to 22.5)	5.3 (3.0 to 9.1)	3.0 (2.1 to 4.3)	2.2 (1.8 to 2.8)	1.7 (1.5 to 2.0)	<0.0001
	recurrent	1.9 (0.9 to 4.1)	1.4 (0.9 to 2.1)	2.3 (1.8 to 2.9)	1.4 (1.2 to 1.7)	1.5 (1.3 to 1.7)	0.1357
O	Brain event first-ever	31.5 (13.7 to 72.5)	7.4 (4.4 to 12.3)	3.0 (2.1 to 4.4)	2.4 (1.9 to 2.9)	1.7 (1.5 to 1.9)	<0.0001
	recurrent	1.9 (0.4 to 8.0)	1.0 (0.3 to 3.3)	1.3 (0.7 to 2.3)	1.4 (1.0 to 2.0)	1.3 (1.0 to 1.6)	0.8530
M	Periphery event first-ever	19.2 (2.5 to 145.9)	11.1 (5.0 to 24.7)	6.7 (4.1 to 11.1)	3.7 (2.7 to 5.1)	2.0 (1.6 to 2.5)	<0.0001
	recurrent	—*	—	—	—	—	—

N	recurrent	1.7 (0.2 to 13.7)	1.1 (0.5 to 2.4)	0.6 (0.4 to 1.2)	1.1 (0.8 to 1.5)	0.9 (0.7 to 1.1)	0.8577
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*No events in these age-groups.

For peer review only

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4 Figure 1 A-F. Age-specific rates for hospitalised coronary, brain and periphery ischaemia by
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6 other vascular history (OVH; yes/no) in men (A,C,E) and in women (B,D,F),
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For peer review only

Title: Cross vascular risk for first and recurrent hospitalised atherothrombosis determined retrospectively from linked data

Short Title: Cross vascular disease risk

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Structured Abstract

Objectives – To determine sex and age-specific risk ratios for first-ever and recurrent hospitalisation for cerebrovascular, coronary and peripheral arterial disease in persons with versus without other vascular history in Western Australia from 2005-2007.

Design – Cross-sectional linkage study.

Setting – Hospitalised population in a representative Australian State.

Participants – All persons aged 34 to 85 years between 1 January 2005 and 31 December 2007 hospitalised with a principal diagnosis of atherothrombosis.

Data sources – Person-linked file of statutory collected administrative morbidity and mortality records.

Main outcome measures – Sex and age-specific risk ratios for first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery using a 15-year lead-in to determine prior events.

Results – Over 3 years, 40,877 (66% men; 55% first-ever) were hospitalised for atherothrombosis. For each arterial territory, age-specific recurrent rates were higher than the corresponding first-ever rates, with the biggest difference seen in the youngest age groups. For all types of first-ever atherothrombosis, rates were higher in those with other vascular history and risk ratios declined with advancing age (trend: all $P < 0.0001$) and remained significantly >1 even for 75-84 year-olds. Whereas, for recurrent events, rates were marginally higher in those with other vascular history and no risk ratio-age trend was apparent with several not significantly >1 (trend: all $P > 0.13$).

Conclusions - This population study of hospitalised atherothrombosis suggests that rates of recurrence are substantially higher than first-events independent of vascular territory, age and sex. These findings accentuate the necessity for early and sustained active prevention.

Article focus

- Stroke and heart attack dominate the vascular burden
- Vascular disease rates rise steeply with age
- Cross vascular risk is predictive of disease recurrence

Key messages

- First-ever atherothrombosis leads the vascular burden
- The risk of a new vascular event in same or another territory is universally very high
- Target primary and secondary prevention to reduce the population disease burden

Strengths and limitations of this study

- Quantification of new and recurrent vascular risk by disease subtype and prior history
- Excluding the very elderly, non-hospitalised events and underdiagnoses of other vascular disease likely overestimated the dominance of coronary events
- Including non-acute hospitalisations will have increased the absolute event rates but had negligible effect on relative comparisons.

Introduction

Few studies have reported population-based estimates of the rate and determinants of incident and recurrent vascular events of the brain (cerebrovascular disease), coronary (coronary heart disease) and periphery (peripheral arterial disease) collectively. The Oxford Vascular Study[1] indicated that 63% of all atherothrombosis subtypes were incident (first-ever) events, and 37% recurrent. Cerebrovascular events were most common, more than coronary, and all rates rose steeply with age. In contrast, the international REACH Registry[2] of atherothrombotic disease in primary-care suggested that coronary events were most common, and that history of symptomatic atheroma in more than one vascular bed was a strong predictor of higher rates of recurrence in the same and other vascular beds.

We aimed to explore the application of the results from the OXVASC and REACH studies[1,2] in a population-based study of hospitalisations for vascular disease among Western Australians aged 35-84 years between 2005 and 2007. Our specific aims were to determine: (1) the absolute age and sex-specific annual rates of first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery; (2) the independent, significant contributions of atherothrombosis in a different vascular bed to first-ever and recurrent hospitalisations for symptomatic events of the brain, coronary and periphery.

Methods

Setting and data source

We conducted a cross-sectional data linkage study of statutory collected administrative data with no direct participant contact. The demographic profile and main health indices for WA are reflective of the Australian population.[3] Linked public and private hospital morbidity

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7 and mortality data were extracted retrospectively from the WA Data Linkage System which
8 is regularly audited for quality.[4] Person-based records are linked with >99% accuracy using
9 probabilistic matching on standard criteria.[4] A linked file of all hospital admissions and
10 deaths for all persons experiencing a cardiovascular event from 1 January 1990 to 31
11 December 2007 was available. As morbidity data in the very elderly are considered less
12 reliable, event rates are calculated and reported for people aged 35-84 years.
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14 Atherothrombosis diagnoses were identified from discharge records according to the
15 International Classification of Disease (ICD) versions 9-Clinical Modification and 10-
16 Australian Modification.[5] The study was approved by research ethics committees at The
17 University of WA (#RA/4/1/1491) and the Department of Health WA (#2009/18).
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29 *Definition and classification of atherothrombosis categories*

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32 Emergency and elective hospital admissions for brain, coronary and periphery ischaemia
33 were identified from principal diagnoses on the discharge records and are described
34 elsewhere.[6] Briefly, coronary included myocardial infarction, unstable angina, stable
35 angina or other ischaemic heart disease; brain included cerebral infarction, transient
36 ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke
37 or intracerebral haemorrhage; and periphery comprised atherosclerosis of the aorta, renal
38 arteries or arteries of the extremities, unspecified peripheral vascular disease, Buerger's
39 disease or stricture of arteries. Hospital morbidity codes for brain[7], coronary[8] and
40 periphery[9] ischaemia have been previously validated, as have vascular deaths.[10] Hospital
41 transfers were counted as one admission, as were readmissions for the same condition within
42 28 days for coronary, and within one day for each of brain and periphery episodes.
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7 All atherothrombosis hospitalisations between 1 January 2005 and 31 December 2007 were
8 classified by vascular bed (or disease subtype), and as first-ever or recurrent (or event type).
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10 First-ever events were defined as having no hospitalisation in the same vascular bed during a
11 15-year look-back period, otherwise the event was classified as recurrent. The same 15-year
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13 15-year look back period was used to determine the binary variable of prior hospitalisation for other
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15 vascular manifestations. The 15-year look-back period was also used to identify the
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17 comorbidities of diabetes, hypertension, chronic kidney disease, atrial fibrillation, heart
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19 failure, chronic lung disease and cancer. There were <0.001% missing values for any of the
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21 variables used in this study.
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27 *Statistical analysis*

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30 Males and females were analysed separately. For each disease subtype, selected differences
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32 in patient characteristics (age by event type, and first-ever events by other vascular history)
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34 were evaluated using t-tests and χ^2 respectively. Overall proportions of first-ever and
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36 recurrent disease patients with hypertension, diabetes, chronic kidney disease, atrial
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38 fibrillation, heart failure, chronic lung disease and cancer were calculated. Age-specific first-
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40 ever and recurrent rates were calculated for each of brain, coronary and periphery stratified
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42 by other vascular history, using the number of events for that disease subtype over the three
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44 years (2005-2007) as the numerator and the corresponding disease-free (prevalent cases
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46 excluded) or disease-specific WA population as the denominator, respectively. Poisson
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48 regression was used to estimate risk ratios for first-ever and recurrent hospitalisations for
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50 each vascular bed for people with other vascular history compared with people without other
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52 vascular history. Models include sex, 5-year age group, and other vascular disease history.
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54 An interaction term of other vascular disease by 10-year age-group was added to the Poisson
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7 model to test for trend in the risk ratio across age groups. Whilst technically we have
8 estimated rate ratios these are interpreted as 1-year risk ratios as these two ratios are
9 numerically very similar when the rates have small magnitude. Data analyses were performed
10 using SAS (version 9.3),[11] and statistical significance was set at $p < 0.05$.
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14 15 16 17 **Results**

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19 There were 27,156 hospitalisations (53% first-ever) for atherothrombosis in men and 13,721
20 (59% first-ever) in women aged 35 to 84 years between 2005 and 2007 (Table 1). Seventy-six
21 percent of brain admissions were first-ever, whereas just over half were first-ever for
22 coronary and periphery. Coronary patients were younger for both first-ever and recurrent
23 admissions compared with their brain and periphery counterparts. The percentage of cases in
24 the 75-84 year age group varied from a low of 17% in men for first-ever coronary event, to a
25 high of 56% in women for recurrent brain events. Hypertension was the most common
26 comorbidity followed by diabetes and chronic kidney disease. Periphery patients were less
27 likely to be admitted acutely and more likely to undergo angiography and/or invasive
28 intervention than brain or coronary patients.
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42 Coronary admissions dominated first-ever (67% in men and 61% in women) and recurrent
43 hospitalisations (80% in men and 77% in women) for atherothrombosis (Table 1). Only 6%
44 of first-ever coronary events in men and women had a prior admission for other vascular
45 disease, compared with first-ever brain (27% men, 18% women) and first-ever periphery
46 (44% men, 30% women) hospitalisations. Recurrent events were more likely than first-ever
47 events to have a history of vascular disease in another vascular bed.
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Atherothrombosis event rates and risk ratios

Figure 1 shows sex and age-specific first-ever and recurrent hospitalisation rates for each disease subtype by history of other vascular disease. Age-specific rates ranged from about 3/1000 for first-ever brain event with no other vascular history to about 200/1000 for recurrent coronary event with other vascular history. For each vascular bed, age-specific recurrent rates in those with and without other vascular history were higher than the first-ever rates, with the biggest difference seen in the youngest age groups. For first-ever atherothrombosis, rates were generally higher in those with other vascular history compared with no other vascular history, particularly in the youngest age groups. There was little difference between those with and without other vascular history for recurrent rates, a trend seen across all age groups, although there were no recurrent hospitalisations for brain or periphery ischaemia involving another vascular territory in the 35-44 year age group in men.

Table 2 shows sex and age-specific risk ratios for first-ever and recurrent hospitalisation by disease subtype comparing persons with other vascular history to those without. The highest risk ratios were for first-ever brain hospitalisations in women 35-44 years (risk ratios 31.5, 95% CI 13.7 to 72.5) and for first-ever periphery event in men and women 35-44 years (risk ratios 21.7, 95% CI 6.3 to 75.1; risk ratios 19.2, 95% CI 2.5 to 145.9, respectively), although confidence intervals were wide. The risk of a first-ever event was greater for those with versus without other vascular history in all age groups, however risk ratios for all first-ever disease subtypes declined with advancing age (trend: all $P < 0.0001$). Risk ratios for recurrent hospitalisations were smaller than for first-ever hospitalisations and several (including all risk ratios for recurrent periphery event) were not significant. Further, risk ratios for recurrent hospitalisations showed no trend with advancing age (trend: all $P > 0.05$).

Discussion

This nationally representative population study of 40,877 first-ever and recurrent hospitalised atherothrombosis documents sex and age-specific risk ratios by vascular bed and history of other vascular disease. The majority of hospitalisations are first-ever, led by coronary, then brain and least for periphery; whilst first-ever rates without a history of other vascular disease rose steeply with age. Recurrent hospitalisation rates in men and women for any disease subtype are substantially higher than the corresponding first-ever rates, although narrowed with advancing age. A history of other vascular disease was associated with a high risk of a new event in another vascular bed in younger men and women. In contrast, a history of other vascular disease had little influence on recurrent events of any type and at any age. Greater sex and age-specific risk ratios occurred in first-ever brain and periphery hospitalisations compared with coronary events. There was less variance in risk ratios for recurrent events across disease subtypes. These findings suggest that once atherothrombosis is clinically manifest in any vascular bed, the risk of further events in the same or another vascular location is very high for all ages and both sexes. This reinforces the need for active secondary prevention in all patients with atherothrombotic disease of any type and regardless of age.

Strengths and limitations

Extensive and high-quality person-based linkage of all hospitalised atherothrombosis by other vascular history enabled determination of first-ever and recurrent rates and disease risk ratios.[4] Events were identified from the principal diagnosis at discharge and in-hospital death code where apparent, as previously validated by our group,[7-10] and others.[12] weakness is that the analysis is limited to hospitalisation data and does not control for out-of-hospital deaths. Sex and age-specific findings are largely consistent within and between disease subtypes, although the risk ratio's with wide CIs in 35-44 age groups should be

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7 interpreted with caution. Nonfatal brain/coronary attacks treated in the community were not
8 included in the analyses but are expected to be small in number.[6] Recognised
9 underdiagnoses of peripheral arterial disease and cerebrovascular events may have
10 resulted,[13] thus diluting their relative contribution to the total hospitalised atherothrombosis
11 burden. Excluding the very elderly has likely overestimated the dominance of coronary
12 events at the expense of brain events, as would the associated elective admissions for the
13 diagnostic (e.g. stress testing, coronary angiography) and coronary revascularisation
14 procedures. The inclusion of non-acute hospitalisations for greater coverage of elective
15 procedures will have increased the absolute rates of events but had negligible effect on
16 relative comparisons.
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29 *Comparisons with other studies*

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32 The age distribution and medical profile of each disease subtype in this representative
33 Australian study are consistent with other hospitalised population studies for myocardial
34 infarction [14,], stroke [15] and peripheral arterial disease.[16] We found little difference in
35 recurrent rates by sex and age, which is entirely consistent with the non-uniform findings of
36 others.[18, 17-20] Differences in methodology likely account for the variability, including:
37 sample size, case definition, all hospitalisations, age restrictions, ethnicity, risk factor profile,
38 duration of follow-up and adjustment for covariates.
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47 The comprehensive population OXVASC study [1] confirms that the majority of
48 atherothrombosis is incident (63% versus 57% in the present study), but led by stroke in that
49 population, and that rates rise steeply with age. The large multinational REACH Registry
50 suggests coronary events dominate the atherothrombosis burden and supports incremental
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7 higher rates with other arterial disease involvement.[21] In a separate REACH analysis[13],
8 patients with peripheral disease experienced lower atherothrombosis rates than patients with
9 stroke or coronary disease, independent of other vascular history. There were no differences
10 in atherothrombosis rates by gender, possibly due to low enrolment of women in that
11 study.[22] Two smaller studies, the SIRO trial [23] and MITICO study [24] reported stroke
12 patients with polyvascular disease had higher rates of recurrence. For co-morbidities, high
13 proportions of first-ever or recurrent atherothrombosis with hypertension, diabetes and
14 chronic kidney disease have been variously identified in population and cohort studies.[15,
15 21, 24-27]
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24 25 26 *Implication of results*

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28 These sex and age-specific rates and risk ratios for first-ever and recurrent hospitalised
29 atherothrombosis by vascular bed and history of other vascular disease permit comparisons of
30 secondary over primary prevention. To minimize the disease burden on the population and
31 hospitals we should aim to prevent the 56% first-ever hospitalisations, in particular for the
32 brain where it is 76%. The prevention of recurrent events is also very important (and not a
33 mutually exclusive) priority, as they contribute a substantial volume of all hospitalisations,
34 about 44%. The substantially higher risk ratios for recurrent events in persons with and
35 without a history of other vascular disease magnify the scope for systematic secondary
36 prevention across disease subtypes.
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49 In Australia, increased uptake and adherence to antiplatelet, blood pressure-lowering and
50 lipid-lowering medication in persons with established atherothrombosis, and long-term anti-
51 smoking campaigns are priority targets for improving cardiovascular outcomes.[28] Two
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7 Australian general practice studies suggest the application of these proven secondary
8 prevention measures continues to be suboptimal.[29, 30] These findings are poignant given
9 the high rates of recurrent events and raised risk ratios in men and women across the age span
10 in the present study. Further, the higher rates of a first-ever admission where there is a history
11 of vascular disease in a different territory, particularly in the younger age groups, necessitates
12 more aggressive treatment of risk factors. [The nationally funded health checks in general
13 practice for 45-49 year olds are an ideal opportunity to effect comprehensive risk assessment
14 and more active primary and secondary prevention in this group.](#) There was no clear gender
15 difference which may be because of the similarly high levels of comorbidities in men and
16 women, or because results were stratified by age, although there may be differences in the
17 over 85 year age group which we have not investigated. [Further,](#) ~~Our~~ findings have potential
18 implications for the management of approximately 0.25 million (4.3% of the population)
19 women and 0.5 million (8.6%) men in Australia hospitalised for atherothrombosis.[6]
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35 Contributing to the high risk ratios of recurrent atherothrombosis in both sexes is that over
36 half are hypertensive and around a quarter variously have diabetes, chronic kidney disease,
37 atrial fibrillation and heart failure, consistent with other studies.[15, 17, 21, 26] Such
38 comorbidities will likely complicate clinical treatment during rehospitalisation and
39 subsequent chronic care.
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48 *Conclusions*

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50 We have shown in a population-based study of hospitalised atherothrombosis that first-ever
51 events predominate and that once vascular disease clinically manifests, the risk of further
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7 events in the same or another vascular bed is very high, even for the young, suppressing the
8 usual demographic effects. These findings highlight the need for greater awareness among
9 clinicians, patients and funders as to the level of risk related to recurrent events and detail the
10 cross-risk associated with a prior hospitalisation in other vascular locations. These findings
11 have important implications for prevention strategies, and the prioritising of resources for
12 service provision and research, and they signal an upward trajectory in absolute numbers of
13 events as the population ages. Data on hospital incidence, recurrence, and event risk ratios
14 across the vasculature will also permit modelling the effect of shared secondary preventive
15 treatments, such as cardioprotective pharmacotherapy and lifestyle changes, on the total
16 burden of hospitalised atherothrombosis.
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Declaration of Conflicting Interests

None Declared

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Contributors

TB, MK, GJH PEN and JH conceived and designed the study; LN, FS, SH, TB prepared the data files for analysis; TB, LN undertook the data analysis and drafted the paper; MK wrote the statistical plan and together with AB provided advanced statistical support; JH, GJH, PEN, PLT, FS provided clinical advice; all authors contributed to interpretation of data, reviewing article drafts, and approving the final manuscript. TB is guarantor.

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Figure 1 A-F. Age-specific rates for hospitalised coronary, brain and periphery ischaemia by other vascular history (OVH; yes/no) in men (A,C,E) and in women (B,D,F), respectively.

For peer review only

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

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p 1, 3 p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5
Objectives	3	State specific objectives, including any prespecified hypotheses	p 5
Methods			
Study design	4	Present key elements of study design early in the paper	p 5.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 5.6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	p 5-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 6.7
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	p 6.7
Bias	9	Describe any efforts to address potential sources of bias	p 6, 10, 1
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7.8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	p 7.8 p 7
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	p 8, Table 1 N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Figure 1
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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	

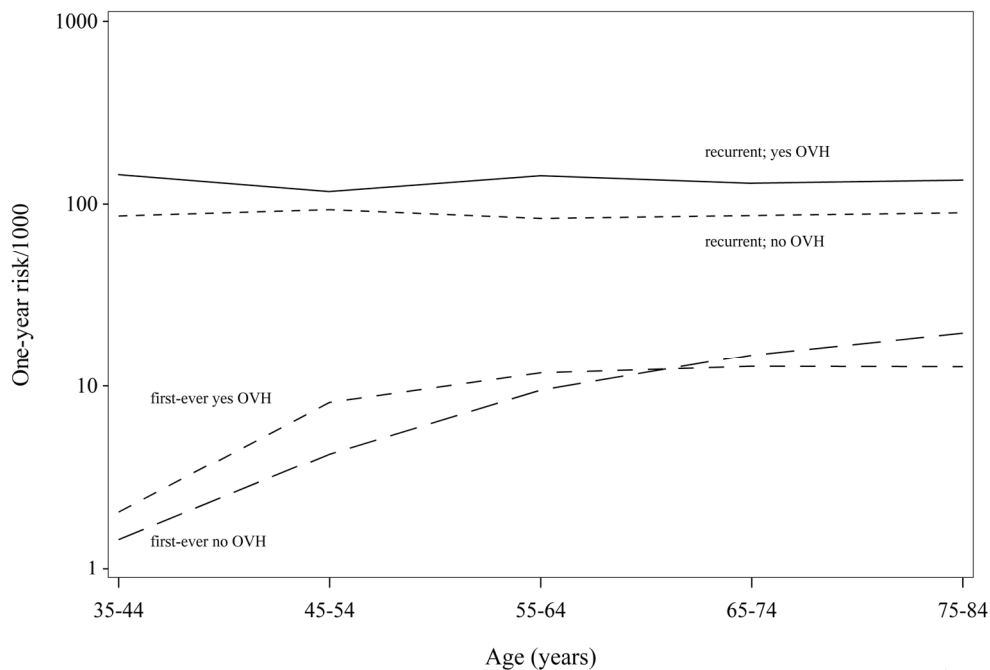
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Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

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*Give information separately for exposed and unexposed groups.

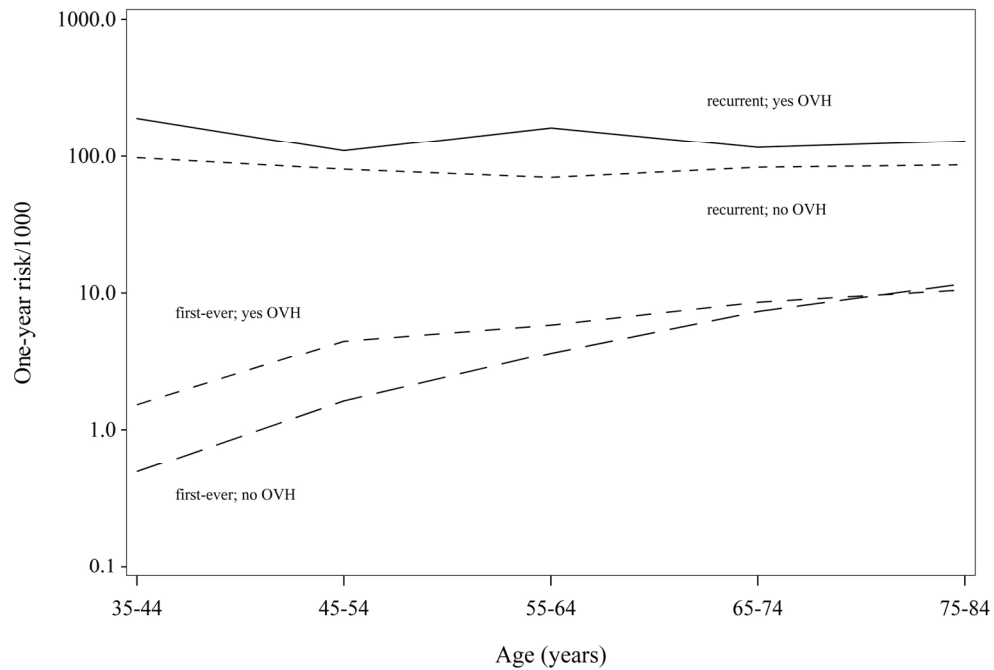
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, 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.



Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in men
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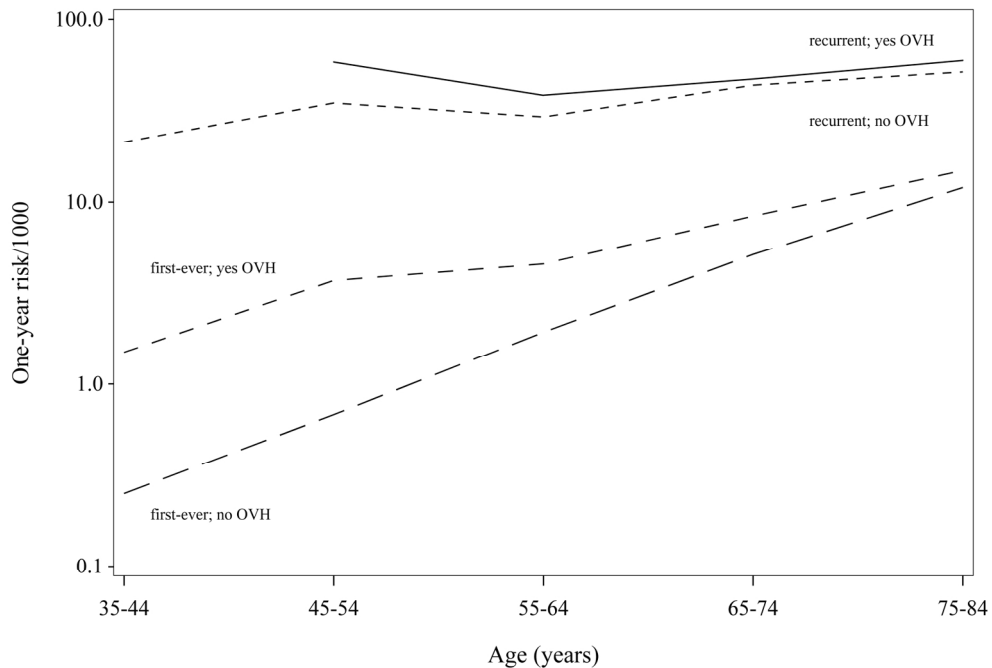
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Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in women
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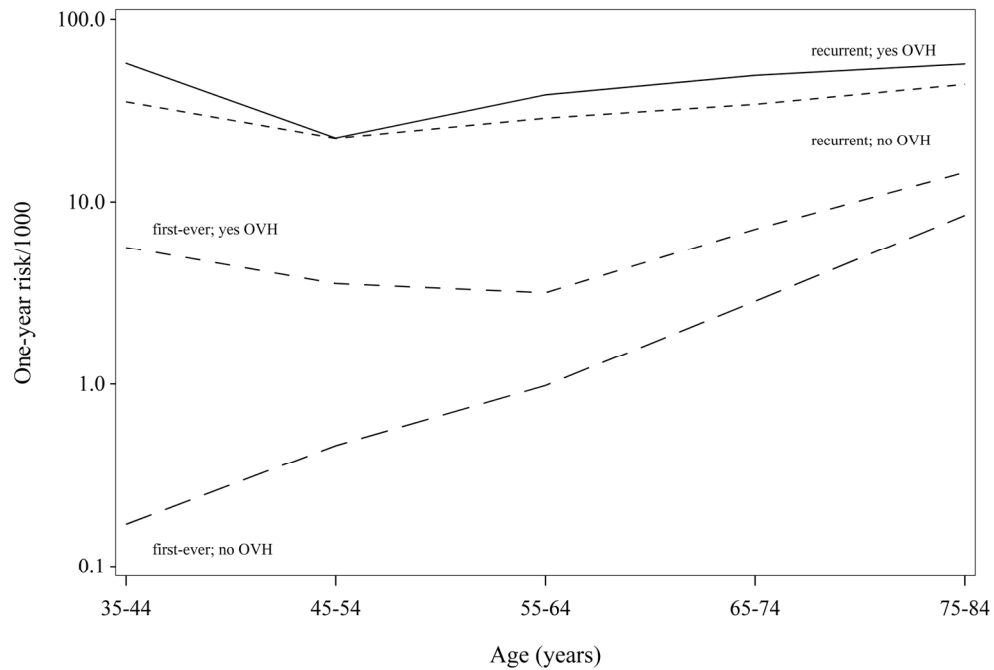
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Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in men
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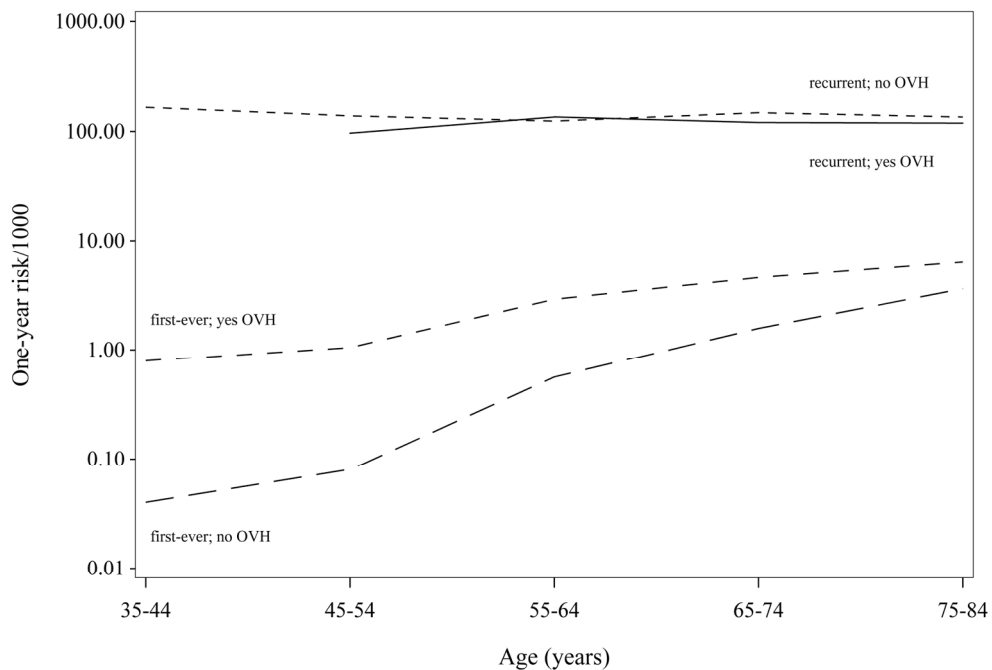
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Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in women
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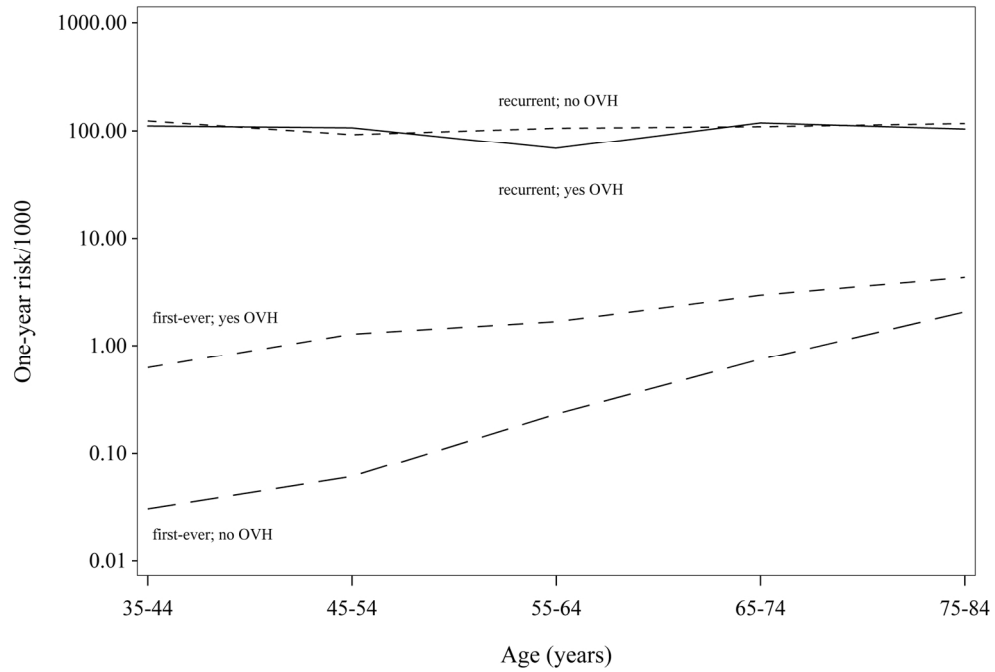


Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in men
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Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in women
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