

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Stroke incidence and association with risk factors in women - a 32-year follow-up of the Prospective Population Study of Women in Gothenburg
AUTHORS	Björkelund, Cecili; Blomstrand, Ann; Blomstrand, Christian; Ariai, Nashmil; Bengtsson, Calle

VERSION 1 - REVIEW

REVIEWER	Raphael Carandang University of Massachusetts Memorial Medical Center, USA
REVIEW RETURNED	22-Apr-2014

GENERAL COMMENTS	<p>The authors should be commended for continuing to study this important topic in women given the disparities in large epidemiological studies of stroke incidence, severity among men and women.</p> <p>It also illustrates the limitations of utilizing ICD codes for classification of stroke types and the need for further validation of cases when using this type of data.</p> <p>Some clarifications/questions:</p> <ol style="list-style-type: none">1. Why are the incidences of different studies so disparate? Ranges from 64-448 per 100,000.2. Should the conclusion include the association/increased risk of DM, HTN, AFib and BP levels?3. Do the authors have any thought on why cholesterol was not associated with stroke in this cohort? <p>Although the authors describe the details of the follow up, and acknowledge the limitations of the registry - they fail to emphasize the importance of the ascertainment methods simply stating that the weakness is the limited number of participants and lack of community and primary care registries. This is a major weakness when describing incidences and results in significant underestimation of incidence.</p> <p>The paper is important given that it studies women specifically but its findings are not novel and have been described in other studies. The paper could refine its writing and conclusions.</p>
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REVIEWER	Andreas Terént Uppsala University Hospital Sweden
REVIEW RETURNED	23-Jun-2014

GENERAL COMMENTS	<p>A cohort of 1462 women aged 38 to 60 years, who lived in Sweden, a high-income country, in the years 1968-9. These women were followed until the years 2000-1. At baseline, i.e. 1968-69, detailed data were collected regarding cardiovascular, reproductive, mental and functional health. The women have been re-examined after 6, 12, 24 and 32 years, but data from these re-examinations are not included in the present study.</p> <p>In the present study, hospital discharge diagnoses of stroke and TIA occurring after the baseline examination were validated against the original patient records. This validation was performed in order to achieve uniform diagnosing of stroke subtypes. During so many years, 1968 to 2001, the diagnostic tools available for stroke subtyping, have improved considerably, from clinical investigation supported by lumbar puncture, to CT and MRI imaging of the brain. The diagnoses of the death certificates were also scrutinized.</p> <p>The change in diagnostic tools during the long study period may have caused misclassification of stroke subtype in some individuals. This is indeed acknowledged by the authors of the present paper, who made great efforts to achieve uniform diagnoses.</p> <p>Hazard ratios for stroke were calculated for each risk factor separately, and for all risk factors together. In multivariable analyses, an association was found between ischemic stroke, high BMI, smoking and low educational level, as well as an association between hemorrhagic stroke and physical inactivity.</p> <p>A weak association was found between total stroke risk (ischemic and hemorrhagic stroke combined) and hypertension (defined as blood pressure, BP, $\geq 160/\geq 90$ mm Hg), but not between stroke subtype (ischemic or hemorrhagic) and hypertension. This may seem contradictory to general knowledge, but one has to keep in mind that the majority (79%) of the women who had elevated BP were treated with antihypertensive drugs. It is not reported how well the BP was controlled at re-examination after 6, 12, 24 and 32 years.</p> <p>A gradient was found between BP level at baseline and future stroke risk. Grade 1 hypertension (140-159/90-99) increased the risk for stroke by 40%, grade 2 hypertension (160-179/100-109) by 60% and grade 3 hypertension by 100% ($\geq 180/\geq 110$) compared with normal BP ($<140/<90$). This indicates that the BP was insufficiently controlled in some women.</p> <p>Overall, this paper contains valuable information on the long-term stroke risk among women who lived in a high income country at the end of the 1960s.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1, comments:

The authors should be commended for continuing to study this important topic in women given the disparities in large epidemiological studies of stroke incidence, severity among men and women.

It also illustrates the limitations of utilizing ICD codes for classification of stroke types and the need for further validation of cases when using this type of data.

Some clarifications/questions:

1. Why are the incidences of different studies so disparate? Ranges from 64-448 per 100,000.

Answer: Great differences are due to several factors such as ages in different populations, ethnic and socioeconomic differences, varying criteria for stroke and different access to hospital facilities for securing diagnoses. In this study an almost complete data base was achieved through combined data from defined timed examinations in the Population Study of Women in Gothenburg and hospital diagnoses from the National Patient Register in Sweden where very few acute stroke cases are cared outside hospitals.

2. Should the conclusion include the association/increased risk of DM, HTN, AFib and BP levels?

Answer: We agree and have added this to conclusions in the abstract

3. Do the authors have any thought on why cholesterol was not associated with stroke in this cohort?

Answer: Cholesterol levels appear as a more complicated and overall weaker risk factor for women.

Although the authors describe the details of the follow up, and acknowledge the limitations of the registry - they fail to emphasize the important of the ascertainment methods simply stating that the weakness is the limited number of participants and lack of community and primary care registries. This is a major weakness when describing incidences and results in significant underestimation of incidence.

Answer: We completely agree and have changed the text accordingly (discussion page 14)

The paper is important given that it studies women specifically but its findings are not novel and have been described in other studies. The paper could refine it's writing and conclusions.

Answer: We are grateful for valuable suggestions and have made changes accordingly.

Reviewer: 2

A cohort of 1462 women aged 38 to 60 years, who lived in Sweden, a high-income country, in the years 1968-9. These women were followed until the years 2000-1. At baseline, i.e. 1968-69, detailed data were collected regarding cardiovascular, reproductive, mental and functional health. The women have been re-examined after 6, 12, 24 and 32 years, but data from these re-examinations are not included in the present study.

Answer: We choose to study baseline data but for further studies these data would be of interest to present and discuss.

In the present study, hospital discharge diagnoses of stroke and TIA occurring after the baseline examination were validated against the original patient records. This validation was performed in order to achieve uniform diagnosing of stroke subtypes. During so many years, 1968 to 2001, the diagnostic tools available for stroke sub-typing, have improved considerably, from clinical

investigation supported by lumbar puncture, to CT and MRI imaging of the brain. The diagnoses of the death certificates were also scrutinized.

The change in diagnostic tools during the long study period may have caused misclassification of stroke subtype in some individuals. This is indeed acknowledged by the authors of the present paper, who made great efforts to achieve uniform diagnoses.

Answer: We thank for this positive comment from the reviewer!

Hazard ratios for stroke were calculated for each risk factor separately, and for all risk factors together. In multivariable analyses, an association was found between ischemic stroke, high BMI, smoking and low educational level, as well as an association between hemorrhagic stroke and physical inactivity.

A weak association was found between total stroke risk (ischemic and hemorrhagic stroke combined) and hypertension (defined as blood pressure, BP, $\geq 160/\geq 95$ mm Hg), but not between stroke subtype (ischemic or hemorrhagic) and hypertension. This may seem contradictory to general knowledge, but one has to keep in mind that the majority (79%) of the women who had elevated BP were treated with antihypertensive drugs. It is not reported how well the BP was controlled at re-examination after 6, 12, 24 and 32 years.

Answer: Blood pressure levels were measured at all scheduled follow-ups in the population study as was also hypertension treatment. We agree with the reviewer that a large part of the women with high blood pressure got treatment. The principles for blood pressure treatment earlier were followed and accordingly the pressures were well controlled. We aimed to study baseline BP in relation to later stroke risk. The rigorous follow up and treatment of the individuals with hypertension in this study, which is one of few interventions in the study, has probably caused that there is an underestimation of the estimated association with stroke.

A gradient was found between BP level at baseline and future stroke risk. Grade 1 hypertension (140-159/90-99) increased the risk for stroke by 40%, grade 2 hypertension (160-179/100-109) by 60% and grade 3 hypertension by 100% ($\geq 180/\geq 110$) compared with normal BP ($< 140/< 90$). This indicates that the BP was insufficiently controlled in some women.

Answer: We agree that this has been the case with reference to modern guidelines. The low risk for grade 1 hypertension in our study is compatible with the guidelines that life style interventions have high priority in combination with follow up of blood pressure levels.

Overall, this paper contains valuable information on the long-term stroke risk among women who lived in a high income country at the end of the 1960s.

VERSION 2 – REVIEW

REVIEWER	Andreas Terent Department of Medical Sciences Uppsala University Hospital Uppsala Swede
REVIEW RETURNED	03-Sep-2014
GENERAL COMMENTS	I think that "Conclusions" in the abstract might be rephrased. As there are difficulties to separate ischemic and hemorrhagic stroke in retrospect, I would prefer associations between total stroke risk and baseline data only i "Conclusions" i abstract.