Migraine, blood pressure and inflammation in relation to cardiovascular disease and mortality

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Thesis for the degree of Philosophiae Doctor
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To my parents Aðalheiður and Guðmundur

ÁGRIP

Inngangur: Mígreni er algengur tauga- og æðasjúkdómur sem hefur áhrif á um 6% karla og 16-18% kvenna. Mígreni hefur verið lýst sem alvarlegum verk oftast öðru megin í höfði ásamt þungum æðaslætti. Verknum fylgja oft ógleði eða uppköst og í sumum tilvikum sjón og skyntruflanir.

Nær öld er liðin síðan fyrsta rannsóknin á tengslum mígrenis og háþrýstings leit dagsins ljós. Margar rannsóknir hafa fylgt í kjölfarið með misvísandi niðurstöðum. Rannsóknum fer fjölgandi sem sýna samband milli mígrenis og blóðþrýstings en þær sýna þó mismunandi tengsl milli mígrenis og slagbils-, hlébils- eða púlsþrýstings. Sumar rannsóknir hafa sýnt aukið algengi háþrýstings og hækkuð blóðgildi bráðfasaprótínsins CRP (C-reactive prótein) á meðal þeirra sem hafa mígreni en aðrar rannsóknir hafa ekki fundið þetta samband. Háþrýstingur og CRP eru bæði áhættuþættir hjarta- og æðasjúkdóma. Því er nauðsynlegt að skera úr um hvort einstaklingar með mígreni séu í aukinni hættu á hjarta- og æðasjúkdómum.

Sjúkleiki og dauðsföll sem tengjast hjarta- og æðasjúkdómum eru algeng og þungbær heilsufarsvandamál bæði í efnahagslega þróuðum ríkjum sem og vanþróuðum. Ekki hafa verið gerðar margar rannsóknir á langtímaáhrifum mígrenis á dánartíðni, hvorki dánartíðni úr hjarta- og æðasjúkdómum né öllum dánarorsökum. Því er aukin þekking á áhættuþáttum hjarta- og æðasjúkdóma á meðal einstaklinga með mígreni mikilvæg og getur hugsanlega nýst til þess að minnka áhættu af þeirra völdum í framtíðinni.

Aðalmarkmið þessarar rannsóknar var að kanna tengsl mígrenis við hjarta- og æðasjúkdóma og áhættuþætti þeirra í Reykjavíkurrannsókn Hjartaverndar. Fyrstu tvær greinarnar (af fjórum) fjalla um tengsl mígrenis við þekkta áhættuþætti hjarta- og æðasjúkdóma (háþrýsting og CRP) í þversniðsrannsókn. Síðari tvær greinarnar fjalla um langtímaáhrif sem tengjast mígreni, þriðja greininum tengsl við drep í heila og hin fjórða við dánarlíkur úr hjarta- og æðasjúkdómum.

Aðferðir: Gögn úr þremur hóprannsóknum voru notuð til þess að svara hinum ýmsu spurningum þessarar ritgerðar. Þær voru: Reykjavíkurrannsóknin, Reykjavíkurrannsókn „unga fólksins“ og AGES-Reykjavíkurrannsóknin.

Reykjavíkurrannsókn Hjartaverndar er ferilrannsókn sem hófst 1967. Markmið hennar var að kanna hjarta- og æðasjúkdóma með framsýnum hætti en þátttakendur voru slembiúrtak karla og kvenna úr Reykjavík og nágrenni, fædd milli 1907 og 1935. Fyrsta skoðun þátttakenda (n=18903) var að meðaltali árið 1975. Til þess að rannsaka fólk sem væri yngra en þátttakendur Reykjavíkurrannsóknarinnar, var annað úrtak tekið árið 1972 sem ber heitið Reykjavíkurrannsókn „unga fólksins“, en í þeim hópi voru karlar og konur (n=2781) fædd á árunum 1940 til 1954. Loks voru gögn úr AGES-Reykjavíkurrannsókninni notuð til að kanna möguleg langtímaáhrif mígrenis. Í þeim hópi voru 4689 einstaklingar sem höfðu tekið þátt í Reykjavíkurrannsókninni og voru enn á lífi við upphaf AGES rannsóknarinnar. Við fyrstu komu í Reykjavíkurrannsóknina og Reykjavíkurrannsókn unga fólksins svöruðu þátttakendur spurningalista og ýmsar mælingar (meðal annars CRP blóðmælingar) voru framkvæmdar. Greining háþrýstings var byggð á tveimur mælingum: Slagbilsþrýstingi ≥160 mmHg og/ eða hlébilsþrýstingi ≥95 mmHg. Einstaklingar á lyfjameðferð við háum blóðþrýstingi voru einnig skilgreindir með háþrýsting. Höfuðverkur var skilgreindur út frá breyttum „International Headache Society” skilmerkjum sem mígreni, mígreni án áru, mígreni með áru og höfuðverkur annar en mígreni. Mígreni á miðjum aldri var rannsakað með segulómun (MRI) í tengslum við síðkomið heiladrep. Mígreni var einnig rannsakað í tengslum við dánarlíkur, nánartiltekið dánarlíkur: af öllum orsökum, vegna hjarta- og æðasjúkdóma, annarra sjúkdóma en hjarta- og æðasjúkdóma, kransæðasjúkdóma og heilablóðfalls.

Niðurstöður: Aldursleiðrétt algengi mígrenis í Reykjavíkurrannsókn Hjartverndar var 5,7% meðal karla og 16,4% meðal kvenna. Ekki fannst samband milli mígrenis og háþrýstings en tengsl fundust milli mígrenis og blóðþrýstings. Fyrir aukningu í hlébilsþrýstingi um eitt staðalfrávik jukust líkur á að hafa mígreni um 14% hjá körlum og 30% hjá konum. Fyrir aukningu í slagbilsþrýstingi um eitt staðalfrávik minnkuðu hins vegar líkur á að hafa mígreni um 19% hjá körlum og 25% hjá konum. Fyrir aukningu í púlsþrýstingi um eitt staðalfrávik minnkuðu líkur á að hafa mígreni um 13% hjá körlum og 14% hjá konum.

Meðalblóðgildi bráðfasaprótínsins CRP var svipað meðal einstaklinga með mígreni og einstaklinga án mígreinis (0,83 vs. 0,79 mg/l) hjá körlum og (0,87 vs. 0,87 mg/l) hjá konum. Tengsl CRP gilda og mígrenis voru einnig sviðuð meðal þeirra sem fengu kransæðasjúkdóm á eftirfylgnitímanum og þeirra sem ekki fengu kransæðajúkdóm.

Í langsniðshluta rannsóknarinnar voru 2693 konur og 1996 karlar. Meðalaldur var 50,9 ár (bil, 33-65) við fyrstu skoðun (í Reykjavíkurrannsókninni) og 76,2 ár (bil, 66-96) í fyrstu skoðun í AGES-Reykjavíkurrannsókninni. Heiladrep greint með segulómun fannst meðal 39,3% karla og 24,6% kvenna. Algengast var að drepið fyndist í litla heila (21,0% hjá körlum og 14,7% hjá konum). Þegar búið var að leiðrétta fyrir aldri, kyni og eftirfylgnitíma voru þeir sem höfðu mígreni með áru (n=361) í aukinni áhættu á að fá síðkomið heiladrep samanborið við þá sem ekki voru með höfuðverk (leiðrétt líkindahlutfall [OR], 1,4; 95% öryggisbil [CI]; 1,1-1,8). Þetta samband var þó eingöngu til staðar hjá konum (algengi heiladreps var 23,0% hjá konum með mígreni með áru en 14,5% hjá konum án höfuðverkja; leiðrétt OR, 1,9; 95% öryggisbil [CI]; 1,4-2,6). Hjá körlum með mígreni með áru var algengi heiladreps 19,3% en 21,3% hjá körlum án höfuðverkja (leiðrétt OR 1,0; 95% CI; 0,6-1,8). Einstaklingar með mígreni án áru og höfuðverk annan en mígreni voru ekki í aukinni hættu á að fá heiladrep.

Einstaklingar með mígreni með áru (n=1397) voru einnig í aukinni áhættu á dauða af öllum orsökum (kyn- og fjölþáttaleiðrétt áhættuhlutfall, Hazard Ratio [HR] og 95% öryggisbil (1,21; 1.12-1.30) og dauða vegna hjarta- og æðasjúkdóma (1,27; 1,13-1,43), samanborið við einstaklinga án höfuðverkja (n=13071), en einstaklingar með mígreni án áru (n=626) og einstaklingar með höfuðverk annan en mígreni (n=3631) voru ekki í aukinni áhættu. Þegar hjarta- og æðasjúkdómum var skipt upp sást að einstaklingar með mígreni með áru voru í aukinni hættu á dauða vegna bæði kransæða-sjúkdóma (1,28; 1,11-1,49) og heilablóðfalls (1,40; 1,10-1,78). Konur með mígreni með áru voru í aukinni hættu á dauða vegna annarra sjúkdóma en hjarta- og æðasjúkdóma (1,15; 1,04-1,27).

Umræða og ályktanir: Algengi mígrenis í Reykjavíkurrannsókn Hjartaverndar var svipað því sem fundist hefur í öðrum hóprannsóknum. Samband milli mígrenis og háþrýstings fannst ekki. Borið saman við einstaklinga án mígrenis þá fannst samband milli mígrenis og lækkaðs púlsþrýstings, lækkaðs slagbilsþrýstings og hækkaðs hlébilsþrýstings. Blóðgildi CRP voru ekki hærri meðal einstaklinga með mígreni samanborið við þá sem voru án mígrenis. Tengsl CRP gilda og mígrenis voru einnig svipuð meðal þeirra sem fengu kransæðasjúkdóm á eftirfylgnitímanum og þeirra sem ekki fengu kransæðasjúkdóm.

Sú langsniðsrannsókn sem hér var framkvæmd bendir til þess að mígreni með áru á miðjum aldri sé tengt heiladrepi á efri árum. Tengsl voru enn til staðar eftir að leiðrétt var fyrir áhættuþáttum hjarta- og æðasjúkdóma, sem bendir til þess að heiladrepstengslin við mígreni með áru séu óháð þessum hefðbundnum áhættuþáttum.

Ennfremur var sýnt í langsniðsrannsókn með eftirfylgd í yfir 470 þúsund persónuár og meðaleftirfylgd uppá 26 ár að karlar og konur með mígreni með áru voru í aukinni hættu á dauða vegna hjarta- og æðasjúkdóma og af völdum allra orsaka en þeir sem höfðu mígreni án áru voru ekki í aukinni áhættu í samanburði við einstaklinga án höfuðverkja. Þegar hjarta- og æðasjúksómum var skipt upp kom í ljós að einstaklingar með mígreni með áru voru í aukinni hættu á dauða vegna bæði kransæðasjúkdóma og heilablóðfalls. Munur í blóðþrýstingi eða CRP gildum skýrir ekki þá auknu dánartíðni vegna hjarta- og æðasjúkdóma sem fannst á meðal einstaklinga með mígreni samanborið við þá sem voru án höfuðverkja í þessari rannsókn. Konur með mígreni með áru voru í aukinni hættu á dauða vegna annarra sjúkdóma en hjarta- og æðasjúkdóma, ekki vegna krabbameina heldur vegna annarra sjúkdóma en krabbameina og hjartasjúkdóma.

Mígreni með áru er sjálfstæður áhættuþáttur dauða vegna hjarta- og æða-sjúkdóma og dauða af öllum orsökum bæði meðal karla og kvenna en mígreni er mun vægari áhættuþáttur en þekktir áhættuþættir eins og reykingar, sykursýki og háþrýstingur.

Lykilorð: mígreni, blóðþrýstingur, C – reaktive prótín (CRP), heiladrep, hjarta- og æðasjúkdómar

ABSTRACT

Introduction: Migraine is a common neurovascular disorder affecting approximately 6% of men and 16-18% of women. It is characterized by severe, pulsating, mostly one-sided headaches, accompanied by vomiting, nausea and in some cases visual and sensory symptoms.

Almost a decade has passed since the first study was published on the association between migraine and hypertension. Many studies have been published since then, and data still conflict on whether there is an association or not. While there is growing evidence that migraine is associated with blood pressure changes, results vary on the effects on systolic-, diastolic- and pulse pressure levels. Some studies have shown increased prevalence of hypertension and elevated C-reactive protein (CRP) among migraineurs; both are risk factors for cardiovascular disease, while other studies have not found this association. This uncertainty on the risk factor status of migraineurs needs to be addressed in order to identify migraineurs that are potentially at increased risk for cardiovascular disease.

Morbidity and mortality associated with CVD weighs heavily in both developed and developing countries. Studies on the long-term effects of having migraine on CVD- and all-cause mortality are scarce. Therefore, increased knowledge of potentially modifiable risk factors for CVD among migraineurs is of great value and may be used to reduce their CVD risk in the future.

The primary aim of this study was to look at migraine in relation to CVD and CVD risk factors in the population-based setting of the Reykjavik Study. In the first two studies (of four), migraine is studied in relation to its association with established risk factors for CVD (hypertension and CRP) in a cross-sectional analysis. In the latter two studies, the long-term consequences (in terms of brain infarcts and CVD mortality) associated with migraine are studied using a prospective/ longitudinal analysis.

Methods: In order to address the different questions in the current study, three cohort studies were used: The Reykjavik Study, the Reykjavik Study for the Young and the AGES–Reykjavik Study.

The Reykjavik Study is a population-based cohort study established in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland. The cohort included a random sample of men and women born between 1907 and 1935 and living in Reykjavik. The first examination of each person (n=18903) occurred between 1967 and 1991, with the average year of examination being 1975. In order to study subjects younger than the participants in the Reykjavik Study, a new sample was selected in 1972, the Reykjavik Study for the Young. This group comprised equal groups of men and women, 2781 in all, born 1940-1954.

Finally, in order to study the potential long-term consequences of migraine, data from the AGES–Reykjavik Study were used. The AGES-Reykjavik Study consists of 4689 surviving members of the original Reykjavik Study. Questionnaires and clinical measures, including fasting CRP blood levels, were obtained at the first visit in the three cohort studies, first visit data from the Reykjavik Study was used for the AGES participants. The diagnosis of hypertension was based on the mean of two measurements: systolic blood pressure ≥160 mmHg and/ or diastolic blood pressure ≥95 mmHg. Subjects on antihypertensive medication were considered hypertensive. Using a modified version of the International Headache Society's criteria headache was classified as migraine, migraine without aura (MO), migraine with aura (MA), or nonmigraine headache (NMH). Migraine during midlife was studied in relation to late-life presence of infarct like lesions on MRI. Migraine was also studied in relation to mortality, specifically: all-cause, non-CVD, CVD, coronary heart disease (CHD) and stroke mortality.

Results: The age-adjusted one-year prevalence of migraine in the Reykjavik Study was 5.7% for men and 16.4% for women. No clear association between migraine and hypertension was found, but a link between blood pressure (BP) and migraine was evident. For a one standard deviation increase in diastolic BP, the probability of having migraine increased by 14% for men and 30% for women. For a one standard deviation increase in systolic BP, the probability of having migraine decreased by 19% for men and 25% for women. It was also found that for a one standard deviation increase in pulse pressure, the probability of having migraine decreased 13% for men and 14% for women.

Average C-reactive protein levels were similar in migraineurs and nonmigraineurs for men (0.83 vs. 0.79 mg/l) and for women (0.87 vs. 0.87 mg/l). The association between CRP and migraine status was also similar among those developing coronary heart disease during follow-up and those who did not.

For the longitudinal analysis, the participants were 2693 women and 1996 men, with an average age of 50.9 years (range, 33-65) at the midlife interview (i.e., Reykjavik Study) and 76.2 years (range, 66-96) at the late-life interview (i.e., AGES-Reykjavik Study). Infarcts were present on MRI in 39.3% of the men and 24.6% of the women. The most common lesion location was the cerebellum (21.0% in men and 14.7% in women). After adjusting for age, sex, and follow-up time, compared with those not reporting headaches once or more per month (n=3243), those with midlife migraine with aura (n=361) had an increased risk of late-life infarct-like lesions (adjusted odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1-1.8) that specifically reflected an association with cerebellar lesions in women (prevalence of infarcts 23.0% for women with migraine with aura vs. 14.5% for women not reporting headaches; adjusted OR, 1.9; 95% CI, 1.4-2.6 vs. a 19.3% prevalence of infarcts for men with migraine with aura vs. 21.3% for men not reporting headaches; adjusted OR, 1.0; 95% CI, 0.6-1.8). Migraine without aura and nonmigraine headache was not associated with increased risk.

Subjects with migraine with aura (n=1397) were also at increased risk of all-cause mortality (sex- and multivariable-adjusted hazard ratio, HR and 95% confidence intervals) (1.21, 1.12 to 1.30) and CV mortality (1.27, 1.13 to 1.43), compared with subjects with no headache (n=13071), while MO (n=626) and NMH (n=3631) subjects were not. Further examination of CV mortality showed that subjects with MA were at increased risk of both coronary heart disease mortality (1.28, 1.11 to 1.49) and stroke mortality (1.40, 1.10 to 1.78). Women with MA were at increased risk of non-CV mortality (1.15, 1.04 to 1.27).

Discussion and conclusions: The prevalence of migraine in the Reykjavik Study was similar to findings in other cohorts. No clear association was found between migraine and hypertension. It was found that subjects with migraine had lower pulse pressure, lower systolic- and higher diastolic blood pressure, compared with controls. CRP levels were not increased

among migraine sufferers, compared with nonmigraineurs. The association between CRP and migraine status was similar among those developing coronary heart disease during follow-up and those who did not.

The longitudinal analysis suggests that a remote history of migraine with aura is associated with brain lesions commonly found in older populations. Results persisted after controlling for cardiovascular risk factors and history of cardiovascular disease, thus suggesting that the mechanism linking the migraine aura with these lesions is independent of the usual risk factors for ischaemic vascular disease and may be specifically related to migraine with aura.

Furthermore, in the longitudinal analysis with over 470 thousand person-years and a median follow-up of 26 years, men and women with migraine with aura were shown to be at increased risk of all-cause and CV mortality, compared with subjects with no headache, while migraineurs without aura were not at increased risk. When CV mortality was examined further, subjects with MA were at increased risk of both CHD and stroke mortality. The increased risk of CV mortality observed among migraineurs vs. those with no headache in current study was neither explained by differences in BP levels nor differences in CRP levels. Women with MA were at increased risk of non-CV mortality, which was not due to increased risk of cancer but increased risk of non-CV mortality other than cancer.

Migraine with aura is an independent risk factor for cardiovascular and all-cause mortality in both men and women, but is weaker than major established risk factors, such as cigarette smoking, diabetes and high blood pressure.

Key words: migraine, blood pressure, C-reactive protein (CRP), brain infarcts, cardiovascular disease mortality

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ABBREVATIONS

5-HT	serotonin (5-hydroxytryptamin)
AD	anno domini (in the year of the Lord)
AGES	Age, Gene/Environment Susceptibility (– Reykjavik Study)
BC	before Christ
BMI	body mass index
CAD	coronary artery disease
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CRP	c-reactive protein
CI	confidence interval
CGRP	calcitonin gene-related peptide
CHD	coronary heart disease
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
HR	hazard ratio
ICHD-2	International Classification of Headache Disorders version 2, 2004
IHS	International Headache Society
MA	migraine with aura
MO	migraine with no aura
MAP	mean arterial pressure
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis and stroke
MTHFR	methylenetetrahydrofolate reductase
MI	myocardial infarction
MRI	magnetic resonance imaging
NMH	nonmigraine headache
NSAID	nonsteroidal anti-inflammatory drug
P	P-value
PFO	patent foramen ovale
PP	pulse pressure
SBP	systolic blood pressure
OR	odds ratio
RR	relative risk
SD	standard deviation
TIA	transient ischaemic attack
TTH	tension-type headache
WHO	World Health Organization

LIST OF ORIGINAL PAPERS

I. Gudmundsson LS, Thorgeirsson G, Sigfusson N, Sigvaldason H and Johannsson M. **Migraine patients have lower systolic but higher diastolic blood pressure compared to controls in a population-based study. The Reykjavik Study.** Cephalalgia. 2006 Apr;26(4):436-44.

II. Gudmundsson LS, Aspelund T, Scher AI, Thorgeirsson G, Johannsson M, Launer LJ, Gudnason V. **C-reactive protein in migraine sufferers similar to that of non-migraineurs: the Reykjavik Study.** Cephalalgia. 2009 Dec;29(12):1301-10.

III. Scher AI, Gudmundsson LS, Sigurdsson S, Ghambaryan A, Aspelund T, Eiriksdottir G, van Buchem MA, Gudnason V, Launer LJ. **Migraine headache in middle age and late-life brain infarcts.** JAMA. 2009 Jun 24;301(24):2563-70.

IV. Larus S Gudmundsson, Ann I Scher, Thor Aspelund, Jon H Eliasson, Magnus Johannsson, Gudmundur Thorgeirsson, Lenore Launer, Vilmundur Gudnason **Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study.** BMJ. 2010 Aug 24;341:c3966.

DECLARATION OF CONTRIBUTION

Paper I

Gudmundsson and Johannsson designed the study. Sigvaldason analysed the data. Gudmundsson and Johannsson drafted the paper. Sigvaldason and Sigfusson acquired the data. Sigvaldason and Gudmundsson take responsibility for the integrity of the data and the accuracy of the data analysis. Gudmundsson, Thorgeirsson, Sigfusson, Sigvaldason and Johannsson critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

Paper II

Gudmundsson and Gudnason designed the study. Gudmundsson and Aspelund analysed the data. Gudmundsson and Gudnason drafted the paper. Aspelund and Gudnason acquired the data. Gudmundsson and Aspelund take responsibility for the integrity of the data and the accuracy of the data analysis. Gudmundsson, Aspelund, Scher, Thorgeirsson, Johannsson, Launer and Gudnason critically revised the draft for important intellectual content and gave final approval of the manuscript to be published.

Paper III

Scher, Eiriksdottir, van Buchem, Gudnason and Launer designed the study. Sigurdsson, Eiriksdottir and Gudnason acquired the data. Scher, Gudmundsson, Sigurdsson, Ghambaryan, Aspelund, van Buchem and Gudnason analyzed and interpreted the data. Scher drafted the paper. Gudmundsson, Sigurdsson, Ghambaryan, Aspelund, van Buchem, Eiriksdottir, Gudnason and Launer critically revised the manuscript for important intellectual content.

Scher, Gudmundsson, Ghambaryan, Aspelund and Launer did the statistical analysis. Eiriksdottir and Gudnason obtained the funding. Sigurdsson, van Buchem, Gudnason and Launer supervised the study. Scher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Paper IV

Gudmundsson, Scher, Launer and Gudnason designed the study. Gudmundsson and Aspelund analysed the data. Gudmundsson and Gudnason drafted the paper. Aspelund and Gudnason acquired the data. Gudmundsson and Aspelund take responsibility for the integrity of the data and the accuracy of the data analysis. Gudmundsson, Scher, Aspelund, Eliasson, Johannsson, Thorgeirsson, Launer and Gudnason interpreted the data, critically revised the draft for important intellectual content, and gave final approval of the manuscript to be published. Gudmundsson and Gudnason were guarantors.

1 INTRODUCTION

1.1 Ancient tales of headache and its treatment

Tales of headache and its treatment reach back thousands of years. Dating as far back as 9000 years, surgery to alleviate headache was evident in the form of trepanation, which is when part of the scull is removed. This procedure was performed in order to release demons and evil spirits from the head. The evil spirits were believed to be the cause of the headaches and other disorders, such as epilepsy and madness (1).

It is noteworthy that the ancient procedure of trepanation is still being used in preindustrial societies to treat migraine and headache (2). Preindustrial societies are known for using ancient treatment methods, and the fact that trepanation is used today to treat headache supports the theory that this treatment was used in the early days of civilization for the same purpose.

Literature from Sumeria in Mesopotamia from 5000 years ago contains an epic poem about Enke, where the author Nishursag speaks of the "land of Dilmun" (which could be the Garden of Eden or heaven):

> "The sick eyed says not
> I am sick eyed
> The sick-headed (says) not
> I am sick-headed."
>
> Cited in Alverez WC 1963 (3)

This could be the wishful thinking of the author describing the future when he is no longer suffering from blinding headaches.

Some have disputed this description arguing that "sick-eyed" might simply be an eye complaint, and "sick-headed" a headache without other migraine symptoms, such as nausea and vomiting (4). It took a couple of thousands of years (1988 AD) to reach a universal consensus on migraine diagnosis with the International Headache Society's criteria for migraine and other headaches (see the next chapter for more on this).

Another poem from Mesopotamia describes a headache; the poet says:

> "The head throbs,
> When pain smites the eyes
> And vision is dimmed."
>
> Cited in Alverez WC 1963 (3)

This description of a migraine attack is very good even by modern standards (Headache Classification Committee of the International Headache Society 2004) (5).

There are more recent descriptions of migraine treatment although these descriptions are more than 3000 years old:

„The Ebers Papyrus, dating back to about 1200 BC, named after a professor of Egyptology, mentions migraine, neuralgia, and shooting head pains, and is said to be based on earlier medical documents from around 1550 BC. Following the instructions on the papyrus, the Egyptians would firmly bind a clay crocodile holding grain in its mouth to the head of the patient using a strip of linen. The linen bore the names of the gods whom the Egyptians believed could cure their ailments. In actual fact, the process may have relieved the headache by compressing the scalp, and possibly collapsing distended vessels that were causing the pain" (1).

Not even the gods were free from headaches. The sun good Ra was believed to suffer from headache, and the goddess Isis treated Ra with a potion of coriander, wormwood, juniper, honey and opium (2).

Hippocrates was the first to distinguish different types of headache (around 400 BC) and state that the headaches were a true disorder and not a visitation from the gods. Here is an excerpt from one of his case reports:

"...He seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck ... vomiting, when it became possible, was able to divert the pain and render it more moderate" (4).

The physician Galen (131-201 AD) used the word "hemicrania", meaning half of the head, to describe headaches. Hemicrania translated from Greek to Latin became "hemicranium" (2) and was transformed to "megrim" in Old English and migraine in French (6).

Figure 1: An interpretation of the treatment of migraine in 1200 BC. A clay crocodile with magic herbs in its mouth was bound to the patients head. (Drawing by P. Cunningham published in Lance JW. Mechanisms and management of headache Sixth Edition 1998 Butterworth-Heineman (6)).

1.2 Why do some people get migraine?

Numerous studies have shown that migraine attack can be triggered by environmental factors (7, 8). Genes and co-morbidity also play a role (9). There are also studies suggesting that both genes and environmental factors influence a person's susceptibility to migraine (10-13). Knowledge about what induces new-onset migraine is scarce. Blau reported that of 60 (41 female and 19 male) consecutive migraine cases, 29 were able to specify events preceding their first migraine attack, usually by several weeks. These events were physical (e.g., illness) or emotional (loss of a close relative/spouse) or a combination of both (14).

Since then several case reports have been published about new onset triggered by orgasm (15), a brain stem cavernous angioma (16), head injury (17) and use of soy isoflavone supplements (18). New onset of migraine has also been reported in the elderly (19).

New-onset migraine has been studied in relation to transcatheter closure of atrial septal defect or patent foramen ovale. A study of 260 consecutive cases showed that migraine headache attacks occurred in 7% of the patients after the transcatheter closure (20).

Numerous studies show mental stress as the most prevalent trigger of migraine attacks (7, 21-23), but a cohort study of work stress and new-onset migraine among female employees did not show an association between work-related stress (24). This cohort study showed that high effort–reward imbalance might function as a modifiable risk factor for new-onset migraine.

1.2.1 Pathophysiology of migraine – neural or vascular?

The pathogenesis of migraine has been postulated for several centuries, and the theories have moved between primary vascular and primary neural mechanisms. In 1664 Thomas Willis published his hypothesis that "megrim" (migraine) was due to dilatation of blood vessels in the head, which gave birth to the vascular theory (25, 26). In the 19th century a conflicting theory was proposed, where the prime event was neurological dysfunction. In 1873, Edward Liveing proposed that migraine was due to "nerve storms evolved out of the optic thalamus" (25).

In 1948 Harold G Wolff proposed that the neurological symptoms of migraine aura were caused by reduced cerebral blood flow due to vasoconstriction. The vasoconstriction would be followed by compensatory vasodilatation, resulting in perivascular oedema and inflammation, which would lead to migraine headache (27). This hypothesis was based on the known distension of extracranial carotid branches during migraine and the ability of vasoconstrictive ergotamines to abort acute migraine attack. The vascular theory was the dominant explanation of migraine for nearly 50 years (28), but in 1983 the theory was contradicted when it was demonstrated that blood flow changes similar to the changes occurring in migraine could be produced by electrical stimulation of brainstem structures (29).

This finding revived the neurogenic theory, and studies followed that focused on the association between the trigeminal nerve and cranial vasculature. In 1984 Moskowitz showed that trigeminovascular axons from blood vessels of the pia mater and dura mater produced a sterile inflammatory reaction with pain through release of vasoactive peptides (30), such as calcitonin gene-related peptides, substance P and neurokinin A (31).

In 1941 Lashley described the expansion of his own visual scotoma in migraine and calculated that the visual cortex was being affected by some process advancing at about 3 mm per minute (32). Three years later (1944) Leao described a progressive shutdown of cortical function, known as "spreading depression" (or cortical spreading depression), in animal brains and speculated

that it may be related to the visual disturbances during migraine aura (a zigzag pattern that appears in the visual field sometimes called fortification spectra of migraine) (33). Waves of inhibition move slowly over the cerebral cortex, suppressing normal activity at a speed of 2-3 mm per minute. In accompanying paper Leao described the vasodilatation accompanying (cortical) spreading depression (34).

Olesen et al. showed, using cerebral Doppler blood flow studies, that vasoconstriction did occur, but vasoconstriction did not precede the aura and continued well into the headache phase of the migraine (see Figure 2) (35).

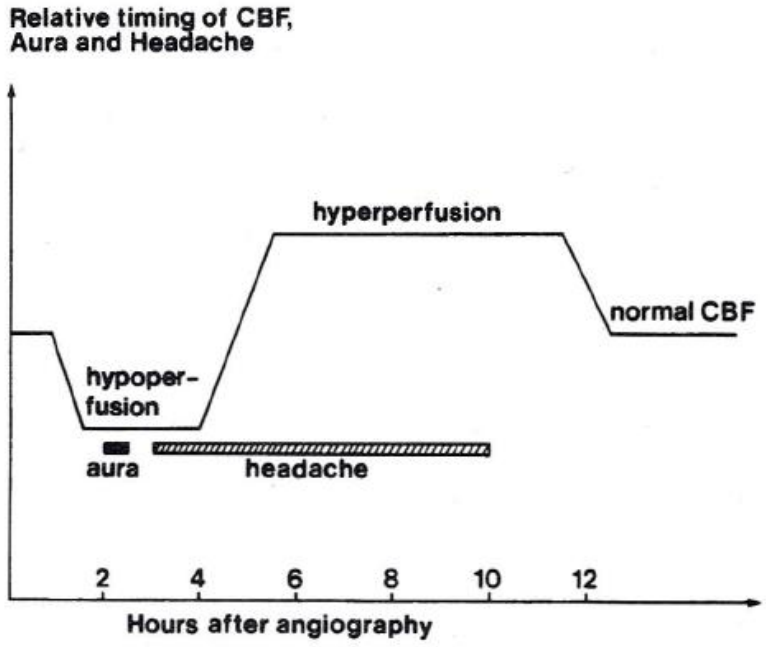

Figure 2: Relationship of aura and headache to changes in regional cerebral blood flow (CBF). (From Olesen et al., Annals of Neurology 1990 (35)).

In the last decade the focus has shifted from the vascular theory toward the neurogenic theory of migraine (36). In the ongoing debate whether the essence of migraine originates in the brain or the blood vessels, it has been proposed that migraine headache can be generated and maintained within the central nervous system, without ever leaving the brain (37), most still consider the disorder to be neurovascular (38).

1.3 Migraine diagnosis

There is no test, biological or imaging, that can pinpoint migraine. The best diagnosis is done by a neurologist or a general practitioner experienced in the field of migraine. The diagnosis is largely based on taking a thorough medical history.

In 1988 a universal consensus was reached in migraine diagnosis. This was a substantial improvement, which made the diagnosis more reliable. From 1962 to 1987 the description of migraine was the following from the Ad Hoc Committee on Classification of Headache:

"Vascular Headaches of Migraine Type. – Recurrent attacks of headache, widely varied in intensity, frequency and duration. The attacks are commonly unilateral in onset; are usually associated with anorexia and, sometimes, with nausea and vomiting; some are preceded by, or associated with, conspicuous sensory, motor, and mood disturbances, and are often familial"

Compared with the 1988 International Headache Society's (IHS) Criteria description, the Ad Hoc Committee's, 1962 (39), is rather vague and does not offer guidance to actual criteria.

1.3.1 Migraine without aura

Here below are the 1988 IHS criteria for Migraine without aura (40):

A. At least 5 attacks fulfilling B-D
B. Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics
    1. Unilateral in location
    2. Pulsating quality
    3. Moderate or severe intensity (inhibits or prohibits daily activities)
    4. Aggravation by walking stairs or similar routine physical activity
D. During the headache at least one of the following
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia

* In children below age 15, attacks may last 2-48 hours. If patient falls asleep and wakes up without migraine, duration is until time of awakening.

Figure 3 graphically shows the symptoms of migraine without aura. Previous terms for migraine without aura were: Common migraine and hemicrania symplex. In addition to the table above, there are other disorders that need to be ruled out before making a definitive migraine diagnosis. For example, history, physical- and neurological examinations do not suggest: headache associated with head trauma, vascular disorders, non-vascular intracranial disorder, substances or their withdrawal, non-cephalic infection or metabolic disorder. Also, headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures (40).

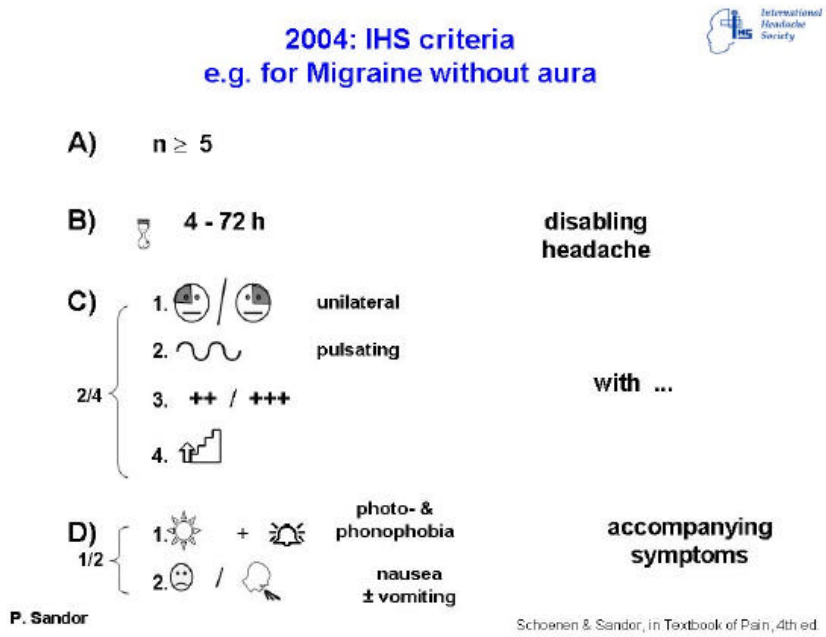

Figure 3: Migraine without aura symptoms shown graphically. (In Schoenen & Sandor, textbook of Pain, 4th ed. (41)).

The IHS criteria were developed through expert consensus rather than any one study or set of studies (42). The 1988 IHS criteria were revised in 2004 with additional diagnostic criteria on chronic daily headache (Hemicrania Continua and New Daily Persistent Headache); sections on Medication Overuse Headache were expanded, and sections on paediatric headache were expanded (43).

1.3.2 Migraine with aura

The 1988 IHS criteria for migraine with aura, which differ from the criteria for migraineurs without aura, are as follows (40):

A. At least 2 attacks fulfilling B.
B. At least 3 of the following 4 characteristics:
   1. One or more fully reversible aura symptoms indicating focal, cerebral, cortical and/or brain stem dysfunction.
   2. At least one aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession.
   3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
   4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).

Similar to the diagnosis for migraine without aura, there are other disorders that need to be ruled out before making the diagnosis.

What is distinctive for migraine (in regards to other common headache disorders) is that, for most studies, the over-all one-year prevalence of migraine has a female to male ratio of between 2 and 3 (see Table 1).

Stovner et al. did a review of headache and migraine prevalence worldwide, in which they found 48 studies from Europe and 14 from North America showing headache and/or migraine in children/adolescents, adults and in the elderly. Of these studies 18 showed sex-specific prevalence of migraine and/or tension-type headache (see Table 1). Female to male ratio for one-year prevalence was as follows: two studies had a ratio between 1.5 and 1.9 (44, 45); 11 studies had a ratio between 2.0 and 2.9 (46-56); three studies had a ratio between 3.0 and 3.3 (57-59), and one study had a ratio of 4.4 (60). The reason for the high sex ratio in the study of Lyngberg et al. (60) is most likely due to the narrow age range used (25-36 years), which is close to where the sex ratio is at its highest (age 35-45). Two of the studies supported sex-specific prevalence for both migraine and tension-type headache, and it is of note that the sex ratio for migraine is much higher than for TTH in these studies (54, 60). The median female to male ratio for migraine prevalence was 2.5 (in 17 studies), but the ratio for TTH was 1.2 (in 3 studies), see Table 1.

Table 1: Sex specific one-year prevalence of migraine and/or tension-type headache and female to male ratio.*

			Age range	Migraine			TTH		
Country, year	Reference	N	(years)	Females	Males	Ratio	Females	Males	Ratio
Croatia, 2001	Zivadinov	3794	15-65	20.2	13.0	1.5			
Sweden, 2001	Dalhof	1668	18-74	16.7	9.5	1.8			
Norway, 2000	Hagen	51383	>=20	15.6	7.5	2.1			
USA, 1994	Kryst	653	>20	9.8	4.5	2.1			
USA, 1996	Stewart	12328	18-65	19.0	8.9	2.1			
Austria, 2003	Lampl	997	>=15	13.8	6.1	2.3			
France, 1996	Michel	9411	>18	18	8	2.3			
UK, 2003	Steiner	4007	16-65	18.3	7.6	2.4			
Denmark, 1991	Rasmussen	740	15-65	15	6	2.5	63	86	1.4
Hungary, 2000	Bank	813	15-80	6.9	2.7	2.6			
USA, 2001	Lipton	29727	>12	18.2	6.2	2.9			
USA, 2002	Lipton	4804	18-65	17.2	6.0	2.9			
USA, 2004	Patel	8579	18-55	19.2	6.6	2.9			
Canada, 1994	O´Brien	2922	>18	21.9	7.4	3.0			
USA, 1992	Stewart	20468	12-80	17.6	5.7	3.1			
Netherlands, 1999	Launer	6491	20-65	25	7.5	3.3			
Denmark, 2005	Lyngberg	207	25-36	23.5	5.4	4.4	90.4	81.5	1.1
USA, 1998	Scwartz	13345	18-65				44.8	37.7	1.2
						1.5 Min			1.1 Min
						4.4 Max			1.4 Max
						2.6 Mean			1.2 Mean
						2.5 Median			1.2 Median

* Adapted from Stovner et al. Cephalalgia 2007 "The global burden of headache: a documentation of headache prevalence and disability worldwide." Studies included here (n=18) are from Europe and North America on migraine and/or tension-type headache and include adults. TTH: Tension-type headache.

1.3.3 Age-specific migraine prevalence for men and women

When the age distribution of the prevalence of migraine is plotted, a strikingly different picture emerges between men and women. Prevalence at a young age is low and similar for men and women but increases for both with increasing age up to age 35-45, where the peak prevalence of migraine is much higher for women than men (51, 58, 61, 62), (about 3 to 4 times higher). The prevalence falls gradually with aging, and the prevalence curves for men and women meet again at low prevalence for both (see Figure 4).

1.3.4 Relationship between migraine and tension type headache

A review on headache and migraine prevalence worldwide by Stovner et al. showed that migraine is a common disorder. The global prevalence of adults with current migraine and tension type headache was 11% and 42%, respectively, showing how tension type headache has much higher prevalence than migraine (63). Data from the Reykjavik Study and the Reykjavik Study for the Young for current migraine was 11.3%, showing migraine prevalence identical to the global prevalence.

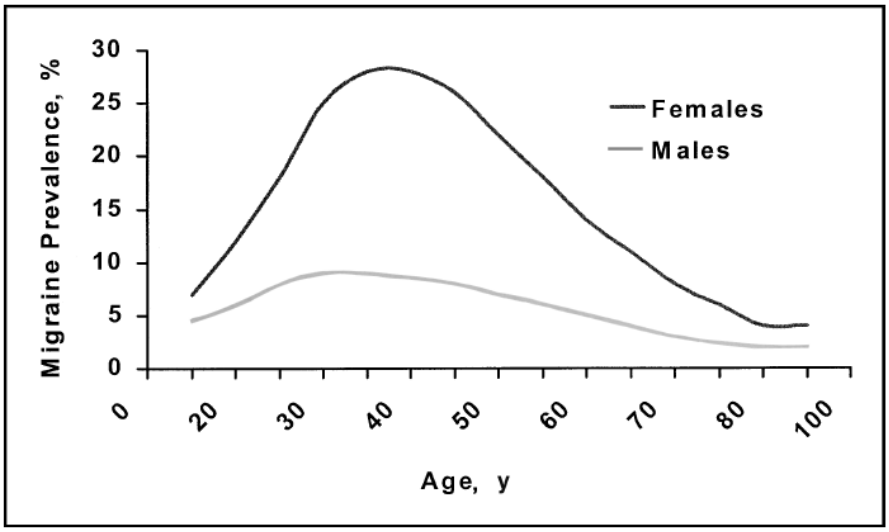

Figure 4: Adjusted age-specific prevalence of migraine by sex, in the United States. From "Prevalence and burden of migraine in the United States: data from the American Migraine Study II" (n=29 727). (By Lipton et al., Headache 2001 (51)).

The similarities and differences for migraine and tension type headache have been described by Borkum:

"In the IHS diagnostic criteria, tension-type headache are, broadly, everything that migraines are not. The pain of tension-type headache is usually bilateral, mild in intensity, continuous, pressing or tightening in quality and not aggravated by routine physical activity. Nausea, vomiting, photophobia (light intolerance), and phonophobia (intolerance for conversational sound levels) are rarely present. At least ten such episodes must have occurred over a person's lifetime to warrant the diagnosis." (43)

In the second edition of the IHS criteria (5) (also called International Classification of Headache Disorders, ICHD-2), there are concerns about migraine being diagnosed as tension type headache and vice versa, that patients coded for episodic tension-type headache included some who had a mild form of migraine without aura, and patients coded for chronic tension-type headache included some who had chronic migraine. These concerns of misclassification would apply especially to patients also having migraine attacks, and some patients may display pathophysiological features typical of migraine. The classification subcommittee attempted to tighten the diagnostic criteria for tension type headache for the second edition, in the hope of excluding migraine patients whose headache phenotypically resembles tension-type headache.

However, this would have compromised the sensitivity of the criteria, and there was no evidence showing the benefits of such a change. A consensus was therefore not reached, but a proposal for new, stricter diagnostic criteria is published under A2 "Tension-type headache" in the appendix of the second edition of the IHS criteria (5).

1.4 Methodological aspects, reliability and validity

Reliability refers to the extent that repeated measurements of a stable phenomenon, by different people and instruments, at different times and in different places get similar results (64). Diagnosis of headache may be unreliable because of varying diagnostic criteria, information obtained and interpretation of information (65).

Validity is the degree to which data measure what they were intended to measure (64). Internal validity is the degree to which the results of a study are correct for the sample being studied. The internal validity is distorted by unreliable measurements, selection bias and confounding factors (64).

External validity is the degree to which the results of an observation hold true in another setting. External validity is also called generalisability (64). The type of study population is important for external validity.

1.5 What is known about migraine and CVD with regard to the current thesis?

An association between migraine and ischaemic vascular events, ischaemic stroke in particular, has been a matter of debate for many years (66). However, an increasing body of publications, in the form of case-control and cohort studies, links migraine, and in particular migraine with aura, with stroke (67). A recent meta-analysis of eight studies (68-71) (four cohorts from one paper, Sternfeld et al. (72)) did not show migraine to be associated with an increased risk of myocardial infarction (67) (Figure 5), but one of the included studies stratifying migraine on aura status found migraineurs with aura at increased risk of myocardial infarction (70).

1.5.1 Migraine and hypertension, migraine and blood pressure

In 1913 Dr. Janeway identified headaches as the main "cerebral" symptom of high blood pressure (SBP>=165 mmHg). Janeway also reported that a surprisingly large number of his hypertensive subjects had been subject to

migraine throughout their lives (73). Since then many studies have been done where headache and migraine have been associated with hypertension (74-78). There have also been studies that have not shown an association (79-81).

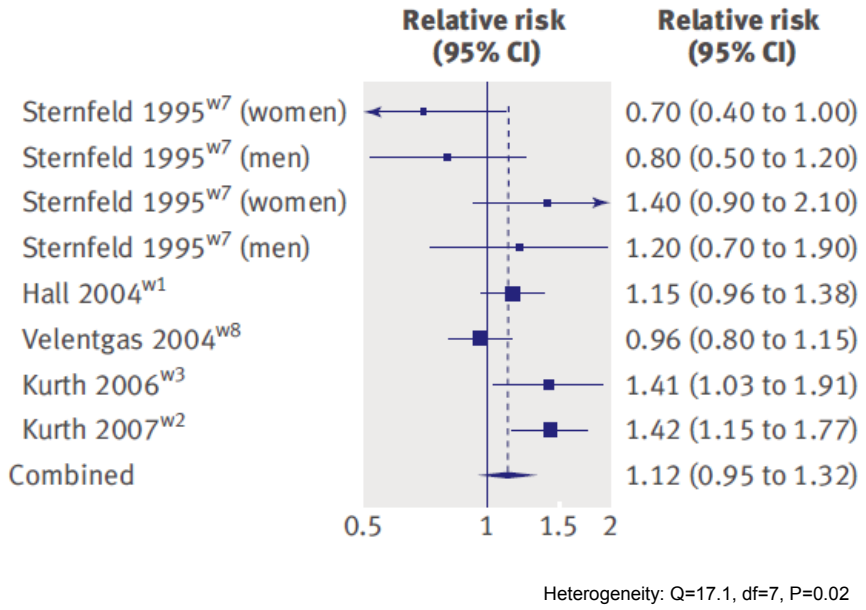

Figure 5: Migraine and risk of myocardial infarction, meta-analysis. (From Schurks et al., BMJ 2009 (67)).

The association between migraine and blood pressure has also been studied, and the findings vary. Case–control studies have shown a positive association between migraine and systolic blood pressure (SBP) (82) and both SBP and diastolic blood pressure (DBP) (83). A cross-sectional epidemiological study examined the relation between DBP and SBP, respectively, in migraineurs and nonmigraineurs. No significant difference in SBP was found, but women migraineurs had higher DBP than nonmigraineurs. This difference was not found for men (80). It has also been found that migraine was more frequent in individuals with normal blood pressure than those with high blood pressure (84). A recent population-based longitudinal study showed that participants with migraine had lower SBP and lower mean arterial pressure than those without headache, and there was a significant trend of decreasing frequency of migraine with increasing SBP (85). Other epidemiological studies have not shown a clear association between blood pressure and migraine (81, 86).

1.5.2 Migraine and C-reactive protein

C-reactive protein (CRP), a marker of inflammation, has been associated with risk of cardiovascular disease (87). CRP has been suggested to be abnormal among migraineurs, possibly through repeated vascular inflammation (88). The risk of stroke and coronary heart disease is greater in migraineurs than in others, especially for those with aura (70, 89). There are limited data on the relationship between CRP and migraine. Welch et al. performed a retrospective review of 60 migraineurs (90% female) with complex clinical features, who were referred to secondary or tertiary clinics (88). The results indicated that 43% of the patients had elevated CRP (defined as >3 mg/l) and suggested a higher proportion in patients without aura (16/29, 55%) than in patients with aura (10/31, 32%).

A case–control study of 50 young adult patients with migraine and 50 controls (78% female) showed that the median CRP level was 1.42 mg/l in migraineurs and 0.90 mg/l in controls (P=0.03) (90).

CRP was higher in the patients without aura than in controls: 2.11 mg/l vs. 0.90 mg/l (P=0.0002). Compared with women with no migraine history, women with a self-reported history of migraine had a modestly increased multivariable-adjusted odds ratio for elevated CRP, in a large cohort study of female health professionals, aged ≥45 years [1.13, 95% confidence interval (CI) 1.05, 1.22] (91). Among current migraineurs, age-adjusted CRP was higher in the women without aura than in women with aura (4.08 vs. 3.86 mg/l).

Thus, the results from these three studies, a clinical report, a case-control study and one large cohort study of female health professionals, suggest that CRP is modestly elevated in migraineurs compared with controls. The results further suggest that the elevation is more evident for migraineurs without aura than those with aura.

1.5.3 Migraine and infarct-like brain lesions

Approximately one-third of individuals with migraine experience neurological aura symptoms before headache onset, and this type of migraine is classified as migraine with aura. The symptoms preceding the migraine attack usually consist of transient visual, as well as sensory, aphasic, or motor disturbances (92). Recent evidence suggests that migraine with aura is associated with an increased risk of clinically evident stroke or coronary artery disease (70, 89, 93-95).

Migraine has also been linked to silent infarct-like lesions, identified on magnetic resonance imaging [MRI], regardless of clinical manifestations, in a community-based cohort evaluated as a part of the CAMERA (Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis) study (96), showing that individuals with migraine were at seven-fold risk of infarcts in the cerebellum, compared with controls; the association was strongest in those with aura and frequent attacks (at least monthly). Although the mechanism linking migraine with aura and vascular disease is uncertain (89, 95, 97), the degree to which migraine is a marker or risk factor for brain changes with potential functional consequences in old age is a question of public health importance.

1.5.4 Migraine and mortality

In recent years, numerous studies have suggested that migraine and migraine with aura, in particular, is a risk factor for clinical and sub-clinical cardiovascular disease (67, 69, 70, 89, 96, 98). Both we and others have examined the relationship between cardiovascular risk factors and migraine, showing differences in risk factors between those with and without migraine (78, 91, 99, 100). Less well-understood is the degree, if any, to which migraine is related to risk of all-cause or cardiovascular (CV) mortality. Only a few articles have been published on migraine and CV or overall mortality, with somewhat conflicting findings, depicting migraine as a risk factor or a neutral or protective factor (67, 68, 70, 71, 101, 102). In a recent meta-analysis (67), due to insufficient data no conclusions could be drawn regarding the risk of mortality associated with migraine with aura.

1.6 Summary

Almost a decade has passed since the first study was published on the association between migraine and hypertension. Many studies have been published since then, and data are still conflicting on whether there is an association or not. There is growing evidence that migraine is associated with blood pressure changes, but results of studies vary on the effects on SBP, DBP and PP. Some studies have shown increased prevalence of hypertension and elevated C-reactive protein (both risk factors for CVD) among migraineurs, which indicates that migraineurs are at increased risk of CVD. Other studies have not found this association. This uncertainty of

migraineurs' risk factor status needs to be addressed in order to identify the migraineurs potentially at increased risk of CVD.

Recent evidence suggests that migraine with aura is associated with an increased risk of clinically evident stroke or coronary artery disease. Although the mechanism linking migraine with aura and vascular disease is uncertain, the degree to which migraine is a marker or risk factor for brain changes with potential functional consequences in old age is a question of public health importance.

Morbidity and mortality associated with CVD weighs heavily on both developed and developing countries (103, 104). Studies on long-term effects of migraine on CVD- and all-cause mortality are rare. Therefore, increasing knowledge of potential modifying factors in the development of CVD among migraineurs is of great value and can hopefully be used to reduce their CV risk in the future. Identifying those at increased CVD risk may open the way to more effective treatment, and unnecessary fear in individuals not at risk for CVD may be avoided.

1.7 Primary aim of this study

The primary aim of this study was to examine migraine in relation to CVD in the population-based setting of the Reykjavik Study

In papers I and II migraine is studied in association with known risk factors for CVD, using cross-sectional analysis, and papers III and IV analyze the long-term consequences of having migraine, using prospective/ longitudinal analysis.

Specific aims of the thesis were to study:

- Migraine and CVD – all the papers are related to this topic (paper I-IV)
- Migraine and hypertension – paper I
- Migraine and blood pressure – paper I
- Migraine and inflammation through C-reactive protein – paper II
- Migraine at middle age and late-life brain infarcts determined with MRI – paper III
- Migraine and CV- , non-CV- and all-cause mortality in a long-term follow-up – paper IV

2 METHODS

2.1 Study Design

Detailed descriptions of the Reykjavik Study (105, 106) have previously been published. In brief, the Reykjavik Study is a population-based cohort study launched in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland (106). The cohort included a random sample of men and women born between 1907 and 1935 and living in Reykjavik. The first examination of each person occurred between 1967 and 1991; the average year of examination was 1975 (Table 2). This cohort was used (or part of it) in all the papers in the thesis. An additional stage (stage VI in Table 2) was added in 1991, where subjects in a group used as a reference until that year who had reached age 70 were examined. This additional stage was included in papers I, II and III.

In order to study subjects younger than the participants of the Reykjavik Study, a new sample was selected in 1972, the Reykjavik Study for the Young (100). This group comprised equal groups of men and women, 2781 in all, born 1940-1954. The subjects were invited to be examined three times in the years 1973-1974, 1983-1985 and in 2001-2003. Those participating in the third stage who had participated in either of the first two stages were sampled and the first visit was used. The age range of the Reykjavik Study for the Young at the time of CRP measurement was 19 to 45. The present analysis is based on the CRP measured at the first examination. The number of subjects that were examined at least once was 1037 men and 1109 women. The average year of examination used was 1975 SD 3.8 years. The cohort of younger subjects was used in papers I and II.

AGES-Reykjavik originates from the Reykjavik Study. A cohort was established in 1967 to prospectively study cardiovascular disease in Iceland. Combining midlife data from the Reykjavik Study and old-age data from the AGES-Reykjavik Study allows a life-course approach to better characterize phenotypes. These combined data can be used to identify patterns of risk factors and evaluate whether these patterns have remained stable or changed with age (107). Participants in the AGES-Reykjavik study were a random sample of participants in the Reykjavik Study that were alive in 2002. This cohort was used in paper III.

Figure 6 is a flow chart of the participation and follow-up in the Reykjavik Study.

Table 2: Cohort recruitment and examination schedule for participants in the Reykjavik Study (1967–1996)* and AGES–Reykjavik (2002–2006).

	Group	B	C	A	D	E	F	
Stage	Cohort Invited	M 2955 W 3101	M 2743 W 2990	M 2755 W 2936	M 2282 W 2429	M 2106 W 2191	M 2081 W 2224	Attended
I	M 1967-68 W 1968-69							M 2203 W 2371
II	M 1970-71 W 1971-72							M 4057 W 4183
III	M 1974-76 W 1977-79							M 5560 W 3900
IV	M 1979-81 W 1981-84							M 3244 W 3587
V	M 1985-87 W 1987-91							M 2592 W 3028
VI	M 1991-94 W 1994-97							M 833 W 1210
AGES *	M & W 2002-2006							M 2421 W 3345

The Reykjavik Study cohort was randomized into six groups or subcohorts (B, C, A, D, E, and F) based on birth dates within month. The Reykjavik Study examinations were conducted in six stages (as listed in the first column), during which different subcohort groups were invited to participate. The total number of invited persons is shown in the first two rows for each subcohort. The following data refer to the number of participants examined at each stage and from each subcohort. The B group was designated for longitudinal follow-up and was examined at each stage. Men and women were examined separately at each stage to optimize examination clinic logistics. Two IDs of the original 30 795 subjects were invalid, and 30 793 subjects were therefore invited.
AGES-Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study.
* Cohort alive in 2002 when recruitment started was M: 4812 W: 6759 (for Men and Women).

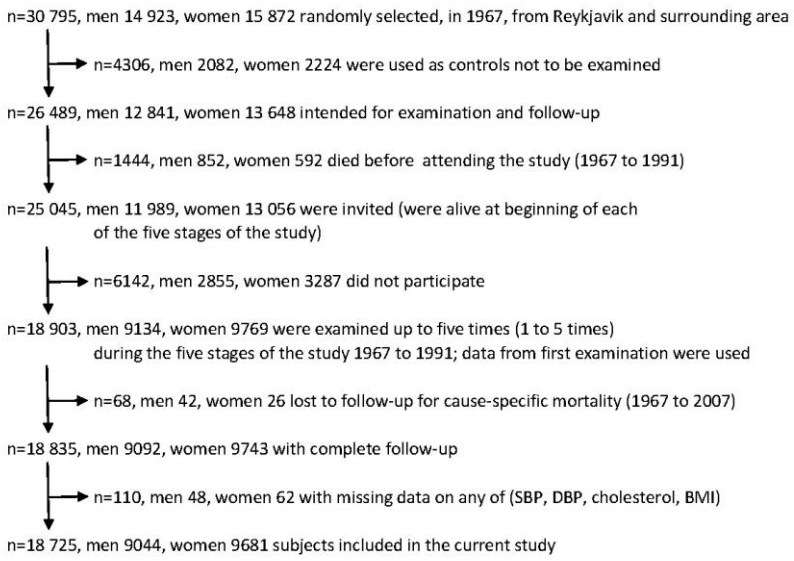

Figure 6: Flow chart of participation and follow-up in the Reykjavik Study. (Paper IV).

2.2 The questions on headache in the Reykjavik Study

The questions were drafted in 1967 when the study started and used throughout the study until 1991.

Questions concerning symptoms during the last 12 months:

Do you get a headache once or more per month?

If YES, please answer the following questions.

1. Is the pain usually on one side of the head?
2. Do you feel nauseated or vomit when you get the headache?
3. Do you get visual disturbances simultaneously or shortly before the pain starts?
4. Do you get photophobia during the headache attack?
5. Do you experience numbness on one side of the face or numbness in either arm before the headache begins?

The studies in this thesis used a modified version of the 1988 International Headache Society (IHS) criteria (40).

In the first paper "*Migraine patients have lower systolic but higher diastolic blood pressure compared to controls in a population-based study. The Reykjavik Study",* migraine was defined as follows:

Subjects were considered to have migraine 'loosely according to IHS criteria' if answering yes to any two or more of questions 1–5.

A 'stricter criterion' was also made where a subject had to answer yes to any three or more of questions 1–5.

In the second paper "*C-reactive protein in migraine sufferers similar to that of non-migraineurs: the Reykjavik Study",* the same definition is used, but migraine is also divided into migraine with and without aura and is as follows:

Subjects were considered to have migraine by "relaxed criteria", if they answered yes to any two or more of questions 1-5 (100). Subjects were considered to have migraine by "strict IHS criteria" if they answered yes to any three or more of questions 1-5 (100). Migraineurs' "relaxed criteria" were visual or sensory symptoms (questions 3 and 5) accompanied by other symptoms. They were further defined as having migraine with aura (MA). Those without visual or sensory symptoms were defined as migraineurs without aura (MO).

No questions were asked about the duration, intensity, phonophobia and pulsating quality of the headache, which are part of the IHS criteria from 1988 (40). Also missing are questions about the less common symptoms of unilateral weakness and speech difficulty.

In order to compare the prevalence of migraine in the Reykjavik Study and the Reykjavik Study for the Young with the prevalence of migraine in other studies we used loose/relaxed criteria for migraine and adjusted the prevalence to age with Segi World population (108, 109).

In the third study "*Migraine headache in middle age and late-life brain infarcts",*

there was a slight change in the definition of migraineurs with aura. All the subjects with migraine with aura in the second study (CRP and migraine) were still considered migraineurs with aura, that is, subjects with headache once or more times per month in the previous year, having visual or sensory aura and one or more migraine symptoms.

The group that was added to the migraineurs with aura group were subjects that had headache once or more per month and had only visual or sensory aura (but none of the other symptoms: headache on one side of the head, nausea or

photophobia). The reason for this addition was that subjects with headache and aura symptoms are likely to have migraine with aura. The questions on migraine symptoms in the Reykjavik Study did not allow for identifying subjects with cluster headache (symptoms: one-sided headache and, in some cases, nausea, sensitivity to light and aura), and these subjects were probably included with the migraineurs. The estimated prevalence of cluster headache and chronic paroxysmal hemicranias combined is 0.5% (110, 111) and is therefore unlikely to affect our results to a great extent.

2.3 Statistical analysis

2.3.1 Migraine and hypertension/ blood pressure (I)

Information on subjects at first visit was used in a logistic regression model. All regression analyses were performed separately for men and women. When calculating odds ratios, adjustments were made for age and year entering the study. Age was entered into the model as a continuous variable and as a categorical variable (12 categories and 6 categories). Comparing the deviance (-2 log likelihood) of the two models, using a Chi square test, age in 12 categories of five years each gave the best fit. Diastolic and systolic blood pressure was introduced separately and jointly to the model. The model containing both systolic and diastolic blood pressure gave the best fit and was therefore used to estimate the effect of systolic and diastolic blood pressure on the odds of having migraine. Pulse pressure (PP) was defined as SBP - DBP and mean arterial pressure as (1/3 SBP + 2/3 DBP).

To see if educational level was a confounder, four educational levels were identified in the questionnaire: elementary school or less, high school education, junior college education and university education, and used in the logistic regression model. Also, to see if smoking was a confounder, smoking was entered into the logistic regression model as: never smoked, former and current smoker.

Collinearity (to see if there was a relationship among the predictor variables that did not involve the response variable) between systolic and diastolic blood pressure was analysed by calculating condition numbers from variance-covariance matrix of the predictor variables and the variance component of each predictor variable.

2.3.2 Migraine and C-reactive protein (II)

We compared average CRP between subjects with migraine (with or without aura) and those without migraine using linear regression. As the distribution of CRP was log-normal, we transformed CRP in all linear regression models.

All regression analyses were performed separately for men and women and performed separately within each age category (19-34, 35-49, 50-59 and 60-81 years). Adjustments were made for case-control status, age, body-mass index (calculated as weight in kilograms divided by height in meters squared, BMI), cholesterol, smoking status (never smoked, former smoker, current smoker), education (elementary school or less, high school education, junior college or university education), current hormone use, current diabetes mellitus, SBP and antihypertensive therapy. Systolic blood pressure (SBP) and antihypertensive use were in three categories: a) SBP<130 mmHg, b) SBP between 130 and 160 mmHg, c) SBP≥160 mmHg and/ or antihypertensive use. For women adjustment was made for oral contraceptive use, which has been shown to be associated with CRP levels (112). Adjustment for physical exercise (defined as 0, 0-5 and ≥6 hours per week) was made, but the other variables listed above were stronger predictors of CRP levels in the regression model, and physical exercise was therefore left out of the final model. In addition, we tested for cohort difference in association of CRP to migraine. The age group represented in both the Reykjavik Study and the Reykjavik Study for the Young was used to estimate a possible cohort effect. A linear regression model with log-transformed CRP as a function of migraine status was used. In a multivariable-adjusted model for men, aged 30 to 39 (n=139 in the Reykjavik Study and n=186 in the Reykjavik Study for the Young), cohort was not a significant variable (P=0.30). Similarly for women (n=84 for the Reykjavik Study and n=62 for the Reykjavik Study for the Young), cohort was not a significant variable (P=0.76) in the model. The above analysis was also performed for subjects that were not diagnosed with a major coronary event during follow-up.

2.3.3 Migraine and infarct-like brain lesions (III)

A priori analyses were conducted for the total sample and stratified by sex. Summary statistics are calculated for the study population overall and by sex. We used logistic regression to estimate the odds (95% CI) of late-life

infarcts in those with mid-life migraine symptoms, relative to those without mid-life migraine symptoms. Separate models were calculated for cerebellar, cortical, subcortical, and total infarcts, for the total sample and by sex. Our model 1 is adjusted for age at the mid-life examination, sex (for analyses on the total sample), and duration of follow-up. In model 2 we additionally adjusted for possible confounding or mediating by mid-life cardiovascular factors.

In secondary analyses, we adjusted for late-life cardiovascular risk factors and stratified by a history of CAD or TIA/stroke, to examine whether these factors changed the associations of migraine with infarcts. We also investigated whether the associations differed by the age at which migraine symptoms were assessed (<50 yrs/ ≥50 yrs).

2.3.4 Migraine and mortality (IV)

After entering the study, subjects were followed for up to 40 years (until the end of 2007). Statistics relating to the cause of death, given by an ICD code, were obtained from Statistics Iceland. The main end-points in the current study were CV, non-CV, and all-cause mortality. Additionally, three CV mortality endpoints were defined: fatal CHD, fatal stroke, and other (e.g., non-CHD and non-stroke) fatal CV disease, based on diagnostic codes as defined in the SCORE project (The Systematic Coronary Risk Evaluation project) (113), except in the current study non-coronary atherosclerotic CV mortality (non-CHD CV mortality) was split into stroke mortality and other CV mortality. An endpoint for fatal CHD was obtained from hospital records, which were systematically reviewed according to the monitoring of trends and determinants in cardiovascular disease (MONICA) protocol (114).

For stroke mortality the following codes were used: International Classification of Diseases, Ninth Revision (ICD-9) codes: 431, 433, 434, 436, 438 and, subsequently, Tenth Revision (ICD-10) codes: I61, I63, I64, I66 and I69.

The total number of subjects at study initiation was n=18 903, of whom 68 subjects (0.36%) were lost to follow-up for cause-specific mortality, and 110 subjects (0.58%) were missing data on blood pressure, cholesterol or body mass index and were omitted, leaving 18 725 subjects (99.1%) with 470 990 years of follow-up, during which 10 358 deaths occurred. For cause-specific mortality, the number of deaths was 4323 for CV mortality and 6035 for non-CV mortality. The 4323 deaths due to CV disease

consisted of 2810 deaths due to CHD, 927 due to stroke, and 586 due to other forms of CV disease.

We used Cox proportional hazards to estimate the relative risk of death (hazard ratio) after adjusting for demographic and baseline CV risk factors. Risk factors for mortality were entered into the Cox model in a stepwise manner, including those with P-values under 0.2 for multi-variable adjustment. For all-cause mortality, adjustments were made for age, body mass index, education (primary, secondary, junior college or university), smoking (no, current, previous), systolic and diastolic blood pressure. For CV mortality the above variables were used in combination with current diabetes mellitus, cholesterol, self-reported history of coronary event, self-reported current antihypertensive medication use and oral contraceptive use for women.

We tested the Cox models for possible violations of the proportional hazard assumption (115, 116). The assumption was not violated except for men with MO when CHD mortality was the endpoint. When subjects were censored after 30 years of follow-up, the proportional hazard assumption held. This resulted in somewhat lower HR for all three headache categories, compared with when the follow-up was up to 40 years. We also used log-minus-log plot. The curves for the groups in the current study were roughly parallel, indicating no violation of the proportionality of the hazard assumption.

We also estimated median life expectancy at age 50 by headache status from a Cox model, adjusting for age only. Men and women were compared descriptively with respect to headache/migraine status and CV mortality through Nelson-Aalen cumulative hazard curves (117, 118). The absolute 10-year risk of all-cause and CV mortality by sex and headache status was estimated from the Cox model at age 50, 60 and 70.

2.3.5 Papers I-IV

Significance testing was two-sided and based on a 5 percent probability level. Thus, results are presented with 95 percent confidence intervals. The software package used was SPIDA (Macquarie University, Australia, Statistical Computing Lab, 1992; paper I), STATA version 9 (StataCorp LP, College Station, TX, USA; papers II-IV) and SAS/STAT software version 9.2.

3 RESULTS

3.1 Study participants

In Table 3 characteristics of the participants in the Reykjavik Study and the Reykjavik Study for the Young can be seen. There are some differences in BP levels between groups, but these differences are not adjusted for age, examination year and antihypertensive medication use. The combined cohort of the Reykjavik Study and the Reykjavik Study for the Young is used in paper I and a nested cohort of CHD cases and controls is used in paper II.

Table 3: Characteristics at first examination of men and women in the Reykjavik Study and the Reykjavik Study for the Young.

	Men			Women		
Characteristics	No migraine Mean ± SD	Loose criteria Mean ± SD	Strict criteria Mean ± SD	No migraine Mean ± SD	Loose criteria Mean ± SD	Strict criteria Mean ± SD
Age	50.6 ± 11.6	47.8 ± 11.0	46.9 ± 11.3	52.2 ± 12.4	47.9 ± 11.4	48.2 ± 10.7
Systolic blood pressure	139.8 ± 18.8	137.0 ± 18.0	136.9 ± 17.3	136.7 ± 20.8	132.8 ± 18.9	132.6 ± 18.1
Diastolic blood pressure	87.3 ± 10.5	86.9 ± 10.6	87.7 ± 10.5	83.1 ± 10.3	82.8 ± 10.6	83.1 ± 10.1
Mean arterial pressure	104.8 ± 12.4	103.6 ± 12.3	104.1 ± 12.2	100.9 ± 12.9	99.4 ± 12.4	99.6 ± 11.9
Pulse pressure	52.5 ± 13.0	50.0 ± 11.7	49.3 ± 10.6	53.6 ± 14.7	50.1 ± 12.8	49.5 ± 12.4
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total number of subjects	9823 (100)	543 (100)	214 (100)	9598 (100)	1573 (100)	826 (100)
Headache	1728 (17.6)	543 (100)	214 (100)	2707 (28.2)	1573 (100)	826 (100)
Pain, unilateral	484 (4.9)	390 (71.8)	175 (81.8)	694 (7.2)	1134 (72.1)	675 (81.7)
Nausea/vomiting	64 (0.7)	241 (44.4)	146 (68.2)	211 (2.2)	1048 (66.6)	667 (80.8)
Visual disturbances	106 (1.1)	314 (57.8)	175 (81.8)	120 (1.3)	812 (51.6)	598 (72.4)
Photophobia	120 (1.2)	327 (60.2)	175 (81.8)	196 (2.0)	1055 (67.1)	698 (84.5)
Numbness	19 (0.2)	116 (21.4)	59 (27.6)	29 (0.3)	367 (23.3)	283 (34.3)
Elementary school or less education	3274 (33.3)	189 (34.8)	67 (31.3)	4895 (51.0)	781 (49.7)	491 (50.7)
High school education	4382 (44.6)	247 (45.5)	106 (49.5)	3789 (39.5)	641 (40.8)	334 (40.4)
Junior college education	1229 (12.5)	70 (12.9)	26 (12.2)	751 (7.8)	125 (8.0)	59 (7.1)
University education	938 (9.5)	37 (6.8)	15 (7.0)	166 (1.7)	26 (1.7)	14 (1.7)
Current smoker	2362 (24.0)	136 (25.0)	56 (26.2)	1505 (15.7)	260 (16.5)	136 (16.5)
Former smoker	5295 (53.9)	295 (54.3)	113 (52.8)	3847 (40.1)	641 (40.8)	321 (38.9)
Hypertension	2728 (27.8)	135 (24.9)	55 (25.7)	2352 (24.5)	313 (19.9)	160 (19.3)
On antihypertensive medication	658 (6.7)	43 (7.9)	21 (9.8)	1063 (11.1)	140 (8.9)	74 (9.0)

The total number of men (*n* = 10 366) and women (*n* = 11 171) in the Reykjavik Study (1967-1996) and the Reykjavik Study for the Young (1973-1985)**.**
Hypertension: blood pressure ≥160 and/or 95 mmHg or on antihypertensive medication. Subjects with the definition 'loose IHS criteria' for migraine (*n* =543 for men and *n* = 1573 for women) include subjects with the definition 'strict IHS criteria' for migraine. (From Paper I).

Table 4: Characteristics of men and women at first examination according to migraine and headache status in the Reykjavik Study (N=18 725).*

	Men					Women				
Characteristic	**No Headache**	**NMH†**	**Migraine**	**MO‡**	**MA§**	**No Headache**	**NMH†**	**Migraine**	**MO‡**	**MA§**
Age, years	52.7 (8.6)	51.5 (8.7)	50.6 (8.2)	49.9 (7.3)	50.8 (8.4)	54.4 (9.0)	52.1 (9.0)	50.7 (8.4)	49.9 (8.1)	51.1 (8.6)
BMI, kg/m^2‖	25.8 (3.4)	25.9 (3.5)	25.6 (3.3)	25.6 (3.2)	25.6 (3.3)	25.2 (4.2)	25.1 (4.4)	24.8 (4.2)	24.7 (4.0)	24.9 (4.3)
Cholesterol, mmol/l¶	6.4 (1.1)	6.3 (1.0)	6.4 (1.1)	6.2 (1.1)	6.4 (1.1)	6.6 (1.3)	6.6 (1.2)	6.5 (1.2)	6.4 (1.2)	6.6 (1.2)
SBP, mmHg**	141.1 (21.1)	139.9 (21.6)	137.9 (20.6)	139.3 (22.5)	137.5 (20.1)	136.8 (22.5)	135.7 (21.8)	133.7 (20.7)	132.3 (19.4)	134.5 (21.3)
DBP, mmHg**	89.3 (11.2)	90.2 (12.3)	88.8 (11.4)	90.6 (12.4)	88.3 (11.1)	84.1 (11.3)	84.3 (11.3)	84.1 (11.4)	83.3 (11.1)	84.5 (11.5)
PP, mmHg**	51.9 (15.0)	49.8 (14.2)	49.1 (13.8)	48.8 (13.8)	49.2 (13.8)	52.7 (16.1)	51.5 (15.5)	49.7 (14.5)	49.0 (13.1)	50.0 (15.2)
Participants n, (%)	7068 (100)	1405 (100)	571 (100)	128 (100)	443 (100)	6003 (100)	2226 (100)	1452 (100)	498 (100)	954 (100)
Headache, %	na††	100	100	100	100	na	100	100	100	100
Pain, unilateral, %	na	30.0	58.0	81.3	51.2	na	26.6	66.9	79.9	60.2
Nausea/ vomiting, %	na	4.1	36.6	66.4	28.0	na	9.2	62.1	79.9	52.7
Photophobia, %	na	6.5	46.2	68.0	40.0	na	6.6	59.0	65.4	55.6
Visual symptoms, %	na	na	63.9	na	82.4	na	na	54.8	na	83.5
Sensory symptoms, %	na	na	21.9	na	28.2	na	na	23.2	na	35.3
Elementary or less education, %	33.4	35.7	37.8	32.8	39.3	54.5	54.0	54.5	49.6	57.0
Hypertension treatment, %	6.8	7.9	8.1	8.6	7.8	11.2	11.8	10.0	7.8	11.1
Current smoking, %	54.9	56.0	56.4	51.6	57.8	40.8	39.7	39.9	35.7	42.0
Former smoking, %	23.4	24.3	23.5	25.0	23.0	15.4	15.3	16.3	17.5	15.6
Medical hormone use, %	0.3	0.4	1.1	0.8	1.1	4.7	7.3	8.9	8.1	8.9
Oral contraceptive use, %	na	na	na	na	na	2.5	4.5	5.5	5.8	5.3
Diabetes, %	4.2	5.1	4.2	5.5	3.8	3.4	2.9	3.4	2.2	4.0
History of coronary event, %‡‡	2.5	1.7	1.1	0.0	1.4	0.8	0.4	0.4	0.4	0.4

Data are means (SD), unless otherwise indicated. * Subjects were originally 18 903, but 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol or body mass index. † NMH: nonmigraine headache, headache without or with one migrainous symptom once or more per month. ‡ MO: migraine without aura, 2-3 of unilateral, photophobia, nausea symptoms. § MA: migraine with visual and/or sensory symptoms. If subject has MO symptoms and MA symptoms, then classified as MA. ‖ BMI: body mass index, body mass in kilograms, divided by height in meters squared. ¶ To convert values for cholesterol to milligrams per decilitre, divide by 0.02586. ** SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure. †† na: not applicable. ‡‡ Coronary event: myocardial infarction, angioplasty or coronary artery bypass graft. (Paper IV).

In Table 4 characteristics of the participants in the Reykjavik Study can be seen (paper IV); part of this cohort participated in the AGES-Reykjavik Study (Paper III).

3.2 Prevalence of migraine in the Reykjavik Study

The crude (unadjusted) one-year prevalence of migraine among men, under loose IHS criteria of migraine, was 5.2%, and for women the corresponding prevalence was 14.1%. The corresponding one- year prevalence of migraine for men, adjusted to Segi World population (108, 109), using loose and strict IHS criteria, was 5.7% and for women the corresponding prevalence was 16.4%. The prevalence of migraine for participants in the Reykjavik Study and the Reykjavik Study for the Young in the same age group (30-39 in Reykjavik Study for the Young and 33-39 in the Reykjavik Study) is similar (see Table 5).

Table 5: Age and sex-specific one-year prevalence of migraine in the Reykjavik Study and the Reykjavik Study for the Young. (Adapted from paper I).

	Reykjavik Young		Reykjavik Study				
Age range	20-29	30-39	33-39	40-49	50-59	60-69	70-79
Men	6.0	10.2	8.9	7.4	6.0	4.1	4.6
Women	19.9	23.1	23.4	19.6	14.1	9.3	7.1

Figure 7 shows that age and sex-specific one-year prevalence of migraine increases with age to about 35 years for both men and women and falls after that.

3.3 Migraine and hypertension (paper I)

Hypertension was not associated with migraine, OR 0.97 (95% CI 0.79, 1.19) for men and 1.03 (95% CI 0.89, 1.18) for women, when using loose IHS criteria. When excluding those on antihypertensive medication, the ORs were lower but not significantly lower than one, OR 0.83 (95% CI 0.66, 1.06) and 0.93 (95% CI 0.78, 1.12), respectively. When dichotomizing on SBP ≥160 mmHg, using loose IHS criteria for migraine (adjusting for age and antihypertensive medication use), there was no association with migraine for men, OR 0.93 (95% CI 0.71, 1.22). However, for women there was a significant inverse association, OR 0.76 (95% CI 0.62, 0.92). When dichotomizing on DBP ≥95 mmHg (adjusting for age and antihypertensive medication use), there was no association with migraine for men or women, OR 0.89 (95% CI 0.71, 1.12) for men and 1.02 (95% CI 0.86, 1.21) for women.

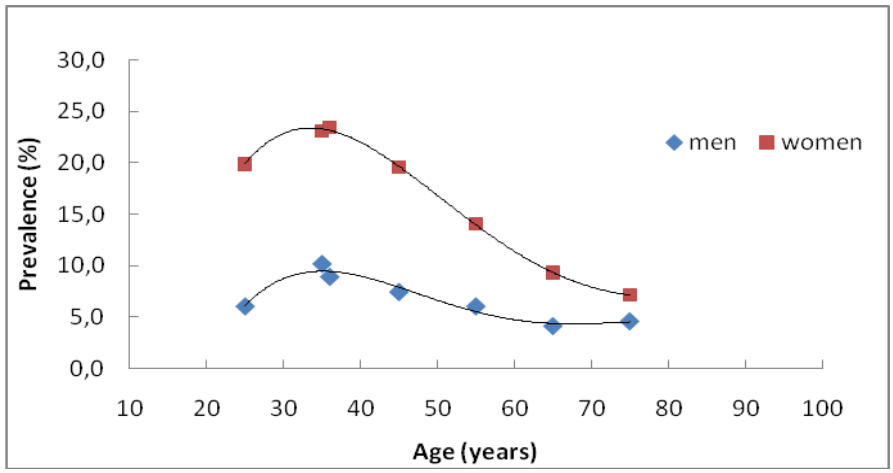

Figure 7: Age and sex-specific one-year prevalence of migraine in the Reykjavik Study and Reykjavik Study for the Young. Prevalence of migraine, defined by a modified version of the 2004 IHS criteria. For both men and women, the first two data points are from the Reykjavik Study for the Young (n=2781), and the next five data points are from the Reykjavik Study (n=18 725). (Adapted from Paper I).

3.4 Migraine and blood pressure (I)

In Figure 8 the association between blood pressure and migraine, using loose and strict IHS criteria of migraine, can be seen. Due to lower sample size in the groups defined by the stricter criteria, the CIs for the odds ratios were wider than for the odds ratios in the groups defined by the loose IHS criteria. SBP was significantly negatively associated with migraine, but DBP was not. There was no significant association between migraine and mean arterial pressure. However, there was a significant negative association between pulse pressure and migraine for both men and women. When looking at the association between SBP and migraine for men and women, adjusting for DBP (see Figure 8), an increase in SBP was associated with decreased prevalence of migraine. On the other hand, when looking at an association between DBP and migraine for men and women, adjusting for SBP (see Figure 8), an increase in DBP was associated with increased migraine prevalence. When SBP and DBP were both in the logistic regression model, there was consistency between using loose and strict IHS criteria of migraine for both men and women. There was a stronger association between blood pressure and migraine amongst subjects defined by strict IHS criteria of migraine than amongst those defined by loose IHS criteria (Figure 8). Comparing the deviance of the regression models for men and women between blood pressure and migraine, the models giving the best fit were those containing

both SBP and DBP and the model containing pulse pressure only, but the model with mean arterial pressure gave the highest deviance (data not shown).

3.4.1 Possible confounders for migraine and blood pressure

The introduction of educational level into the model did not change the association between pulse pressure and migraine significantly and was therefore left out of the model (P for difference in beta coefficients, P=0.99 for men and P=0.93 for women, t-test).

Relative to those who had never smoked, current smoking was not a significantly predictive variable in the model for migraine in relation to age, pulse pressure and antihypertensive medication for men (P=0.91; OR 1.01, 95% CI: 0.81 – 1.27) or for women (P=0.96; OR 0.96, 95% CI: 0.85 – 1.08). In the same model former smoking was not significantly predictive of migraine for men (P=0.20; OR 1.18, 95% CI: 0.91 – 1.54) or women (P=0.13; OR 1.13, 95% CI: 0.97 – 1.32). Smoking was therefore left out of the model. The variables that were used for each sex in the final regression model were age and year of examination. Mean arterial blood pressure, pulse pressure, systolic and/or diastolic blood pressure were all analysed in relation to migraine, adjusting for these variables.

A possible collinearity between systolic and DBP was considered. When checking for collinearity in a logistic regression model, it is advised to check condition numbers that are over 20 and to check the variance component for these values. Further analysis is advised when the variance component exceeds 0.5 for more than one variable, where the condition numbers are over 20. The condition numbers where systolic and diastolic blood pressure had variance component 0.8-0.9 was about 40. When systolic and diastolic blood pressure were normalized (that is, the average was deducted, and the difference then divided by the standard deviation), the regression was almost identical and the deviance also. Where systolic and diastolic blood pressure was dominant, the condition numbers were only about 4, so there was little concern regarding collinearity. Also, the correlation coefficient for systolic and diastolic blood pressure was 0.75, but it is usually close to 0.99 when there is considerable collinearity.

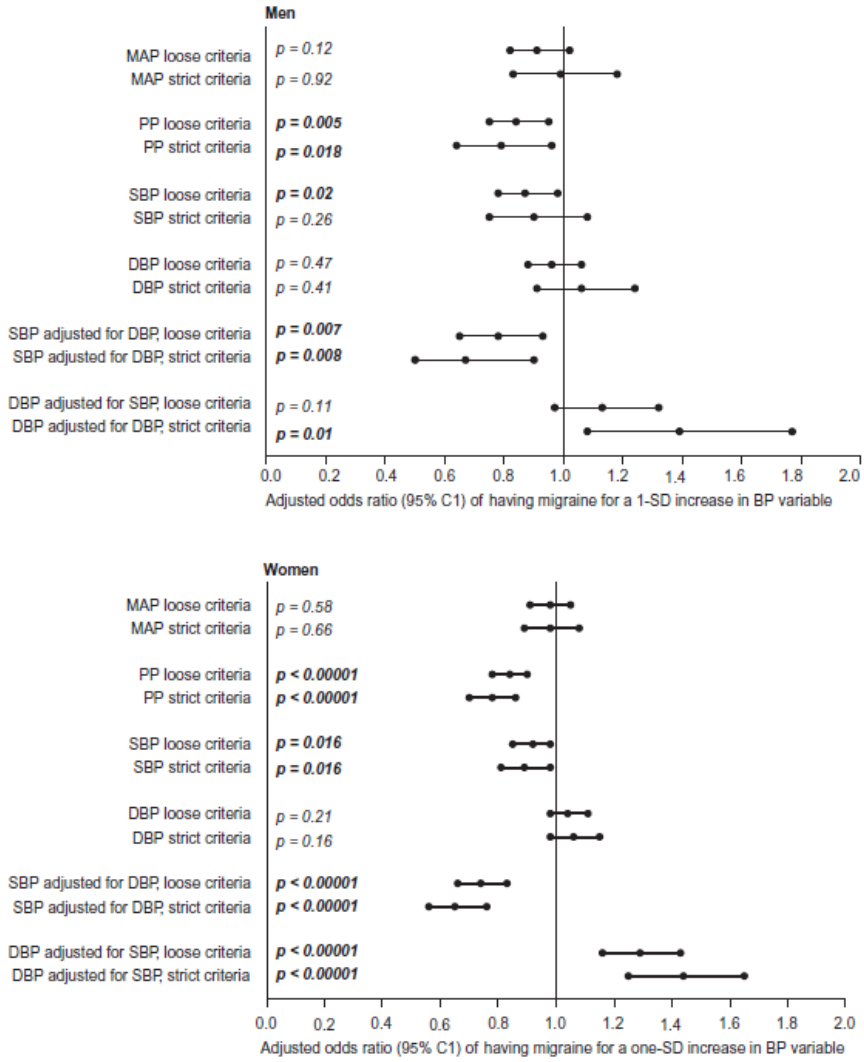

Figure 8: Association between migraine and blood pressure variables. Adjusted odds ratio (95% confidence interval) of having migraine for a 1-SD increase in blood pressure variable. Systolic (SBP) and diastolic (DBP) blood pressure are entered individually and jointly into the regression model. Loose IHS criteria of migraine: answering yes to two or more of five questions on migraine, men (n = 500) and women (n = 1433). Strict IHS criteria of migraine: answering yes to three or more of five questions on migraine, men (n = 193) and women (n = 752). Adjustment is made for age and year of examination. Subjects on antihypertensive medication are excluded. PP, pulse pressure; MAP, mean arterial pressure. Data from the Reykjavik Study and the Reykjavik Study for the Young. (From Paper I).

3.5 Migraine and C-reactive protein (II)

Since the cohort used in paper II was a nested cohort from the Reykjavik Study and the Reykjavik Study for the Young, a comparison of migraine prevalence was made in the nested cohort to the already defined prevalence for the Reykjavik Study (Paper I). The crude one-year prevalence of migraine (relaxed criteria) was 5.0% among men and 14.3% among women. This prevalence was similar to the prevalence of migraine in the whole cohort (5.2% for men, 14.1% for women, Figure 9).

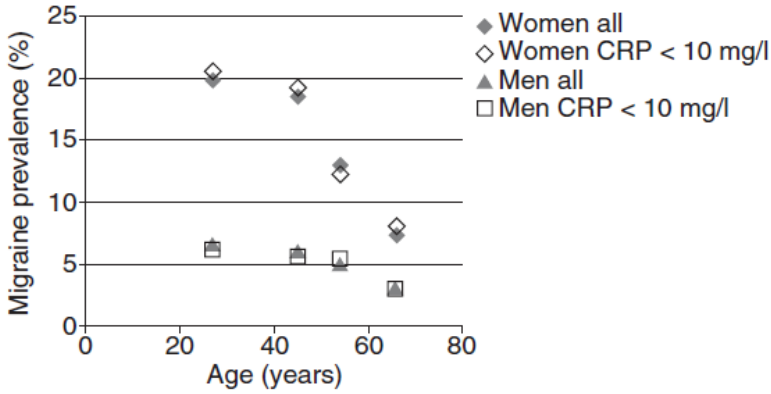

Figure 9: Comparison of the age- and sex-specific one-year prevalence of migraine between those in the current study and the entire cohort. Those with C-reactive protein (CRP) measurements (n = 7251) used in the current study and the entire cohort (n = 21049) of the Reykjavik Study and the Reykjavik Study for the Young (from Paper II).

After excluding subjects with CRP above 10 mg/l (n=313), the median CRP value for all other subjects of the Reykjavik Study (n=5906) was 1.31 mg/l (25th and 75th percentile 0.63 and 2.68 mg/l), and the corresponding median CRP value for the subjects (n=1345) of the Reykjavik Study for the Young was 0.6 mg/l (25th and 75th percentile 0.3 and 1.4 mg/l).

Age-adjusted and multivariable-adjusted CRP values for nonmigraineurs, migraineurs, migraineurs without aura (MO) and migraineurs with aura (MA) are shown in Table 6. The age-adjusted values for men were borderline lower for MO subjects than nonmigraineurs, and values for MA subjects were borderline higher than for MO subjects. These differences were attenuated with multivariable adjustment. For women there were no statistically significant differences between the groups. Multivariate-adjusted values were similar among groups, ranging from 0.70 mg/l to 0.83 mg/l for men and 0.85 mg/l to 0.87 mg/l for women.

Table 6: Age- and multivariable-adjusted CRP values (mg/l) with respect to migraine status, relaxed IHS criteria‡ and sex.

	No Migraine	Migraine	P vs. No Migraine	MO	P vs. No Migraine	MA	P MA vs. MO
Men	n=4551	n=241		n=66		n=175	
Age-adjusted model*	1.31 (1.27-1.35)	1.24 (1.09-1.40)	0.38	1.03 (0.81-1.31)	0.05	1.32 (1.14-1.53)	0.07
Multivariate-adjusted model†	0.83 (0.77-0.90)	0.79 (0.69-0.91)	0.44	0.70 (0.54-0.89)	0.14	0.83 (0.71-0.97)	0.21
Women	n=2102	n=357		n=136		n=221	
Age-adjusted model*	1.17 (1.12-1.23)	1.14 (1.02-1.27)	0.63	1.09 (0.91-1.30)	0.42	1.17 (1.02-1.34)	0.51
Multivariate-adjusted model†	0.87 (0.79-0.97)	0.87 (0.75-0.99)	0.90	0.85 (0.70-1.02)	0.75	0.87 (0.75-1.03)	0.75

MO: Migraine without aura, MA: Migraine with aura.
* Subjects in the Reykjavik Study and the Reykjavik Study for the Young with available CRP measurements. CRP values ≥10 mg/l excluded.
† CRP and migraine status in a linear regression model adjusted for case-control status, age, BMI, cholesterol, smoking, education, hormone use, diabetes mellitus, SBP and antihypertensive therapy. For women adjustment was also made for birth control use. The profile used in the multivariable-adjusted model was: control with average values for continuous variables, non-smoker, high school education, SBP between 130 and 160 mmHg, without: diabetes, hormone use and antihypertensive therapy. Women without birth control use.
All comparisons between MA and No Migraine gave p-values >0.8
‡ Migraine, relaxed criteria, defined as answering yes to 2 or more out of 5 questions on migraine. (From Paper II).

Table 7 shows similar comparison to that in Table 2, but with stricter migraine criteria. The CRP values are almost identical for migraine defined with strict and relaxed criteria.

Table 7: Age- and multivariable-adjusted CRP values (mg/l) with respect to migraine status and sex, using strict IHS migraine criteria‡.

	No Migraine	Migraine‡	P
Men	n=4551	n=92	
Age- adjusted model*	1.30 (1.27-1.35)	1.23 (1.01-1.50)	0.58
Multivariable-adjusted model†	0.83 (0.77-0.90)	0.79 (0.64-0.97)	0.59
Women	n=2102	n=180	
Age- adjusted model*	1.16 (1.11-1.22)	1.09 (0.94-1.27)	0.43
Multivariable-adjusted model†	0.87 (0.79-0.97)	0.87 (0.73-1.03)	0.95

* Subjects in the Reykjavik Study and the Reykjavik Study for the Young with available CRP measurements. CRP values ≥10 mg/l excluded.
† CRP and migraine status in a linear regression model, adjusted for case-control status, age, BMI, cholesterol, smoking, education, hormone use, diabetes mellitus, SBP and antihypertensive therapy. For women adjustment was also made for birth control use. The profile used in the multivariable-adjusted model was: control with average values for continuous variables, non-smoker, high school education, SBP between 130 and 160 mmHg, without: diabetes, hormone use and antihypertensive therapy. Women not using birth control.
‡ Migraine, strict IHS criteria: answering yes to 3 or more out of 5 questions on migraine. (From Paper II).

Table 8 shows age and multivariate-adjusted CRP levels by age. Adjusted CRP levels increased gradually with age. In men CRP levels were consistently lower for MO subjects than nonmigraineurs and MA, but the difference was not significant. In women nonmigraineurs and women with migraine and aura, there was a gradual increase in CRP levels with age. Women with migraine without aura had higher multivariable-adjusted CRP values in the young cohort, age group 19 to 34 years (1.01 mg/l for MO vs. 0.81 mg/l for nonmigraineurs P=0.08), but with increasing age the CRP levels for women migraineurs with no aura gradually decreased, and by age 60 to 81 CRP levels were significantly lower than in migraineurs with aura and nonmigraineurs (0.52 mg/l MO vs. 1.01 mg/l MA, P=0.029; 0.52 mg/l MO vs. 1.07 mg/l control, P=0.007).

Using 3 mg/l as a cut-off for elevated CRP levels and excluding subjects with a history of myocardial infarction, oral contraceptives and other medical hormone use, the proportion of men and women with elevated CRP was similar for subjects with and without migraine, 19.3% and 20.0%, respectively, for men and 14.1% and 16.6%, respectively, for women. When stratifying by migraine aura, the proportion of nonmigraineurs, MO and MA, with elevated CRP were 20.0%, 13.8% and 21.4%, respectively, for men (P=0.43, logistic regression with age adjustment) and 16.6%, 9.7% and 16.8%, respectively, for women (P=0.43).

Table 8: Age- and multivariable-adjusted CRP values and migraine status for men (i) and women (ii) The Reykjavik Study and Reykjavik Study for the Young.

i) Men

Cohort	Average age and range	Migrainestatus	n	Age adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl	Multivariable-adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl
Reykjavik	27	Control	513	0.57 (0.52, 0.63)				0.61 (0.49, 0.76)			
young	19-34	Migraine	34	0.66 (0.46, 0.93)	P=0.47			0.68 (0.45, 1.01)	P=0.55		
		MO	13	0.50 (0.28, 0.89)		P=0.24	P=0.58	0.51 (0.28, 0.92)		P=0.18	P=0.51
		MA	21	0.77 (0.49, 1.21)				0.82 (0.50, 1.35)			
Reykjavik	44	Control	1168	1.14 (1.08, 1.21)				0.71 (0.61, 0.83)			
	35-49	Migraine	67	1.09 (0.87, 1.38)	P=0.72			0.67 (0.51, 0.88)	P=0.63		
		MO	11	1.01 (0.56, 1.82)		P=0.77	P=0.68	0.61 (0.34, 1.09)		P=0.70	P=0.58
		MA	55	1.11 (0.86, 1.44)				0.72 (0.56, 0.92)			
Reykjavik	54	Control	1856	1.30 (1.25, 1.36)				0.74 (0.66, 0.84)			
	50-59	Migraine	105	1.12 (0.93, 1.35)	P=0.12			0.69 (0.56, 0.84)	P=0.26		
		MO	32	0.93 (0.66, 1.32)		P=0.20	0.06	0.62 (0.44, 0.87)		P=0.44	P=0.26
		MA	73	1.21 (0.97, 1.52)				0.72 (0.56, 0.92)			
Reykjavik	66	Control	924	1.56 (1.47, 1.66)				1.16 (1.00, 1.36)			
	60-79	Migraine	27	1.61 (1.14, 2.28)	P=0.86			1.26 (0.88, 1.82)	P=0.64		
		MO	7	1.16 (0.57, 2.39)		P=0.30	P=0.42	0.93 (0.45, 1.90)		P=0.26	P=0.55
		MA	20	1.78 (1.19, 2.68)				1.50 (0.97, 2.31)			

ii) Women

Cohort	Average age and range	Migraine status	n	Age-adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl	Multivariable-adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl
Reykjavik	27	Control	530	0.78 (0.71, 0.86)				0.81 (0.65, 1.01)			
young	19-34	Migraine	137	0.80 (0.67, 0.96)	P=0.83			0.87 (0.67, 1.13)	P=0.44		
		MO	69	0.92 (0.71, 1.19)		P=0.13	P=0.24	1.00 (0.73, 1.38)		P=0.08	P=0.08
		MA	68	0.69 (0.53, 0.90)				0.75 (0.55, 1.03)			
Reykjavik	44	Control	236	0.94 (0.80, 1.09)				0.67 (0.50, 0.90)			
	35-49	Migraine	60	0.81 (0.61, 1.07)	P=0.35			0.66 (0.46, 0.94)	P=0.96		
		MO	21	0.72 (0.44, 1.16)		P=0.54	P=0.24	0.60 (0.36, 0.98)		P=0.56	P=0.63
		MA	39	0.86 (0.60, 1.22)				0.70 (0.46, 1.07)			
Reykjavik	54	Control	716	1.09 (1.01, 1.18)				0.73 (0.62, 0.87)			
	50-59	Migraine	101	1.11 (0.91, 1.36)	P=0.86			0.78 (0.61, 0.99)	P=0.54		
		MO	32	0.86 (0.60, 1.24)		P=0.09	P=0.21	0.66 (0.46, 0.96)		P=0.24	P=0.55
		MA	69	1.25 (0.98, 1.61)				0.85 (0.63, 1.13)			
Reykjavik	66	Control	564	1.52 (1.40, 1.64)				1.07 (0.87, 1.32)			
	60-81	Migraine	50	1.32 (1.02, 1.71)	P=0.31			0.86 (0.63, 1.18)	P=0.11		
		MO	12	0.87 (0.51, 1.49)		P=0.07	P=0.04	0.52 (0.30, 0.91)		P=0.03	P=0.007
		MA	38	1.51 (1.12, 2.04)				1.01 (0.71, 1.43)			

CRP, migraine status, age and gender in the Reykjavik Study and the Reykjavik Study for the Young, using linear regression, adjusting for age, BMI, cholesterol, smoking, education, hormone use, diabetes mellitus, SBP and antihypertensive. Each age category was analysed separately and subjects with CRP values>=10 mg/l were excluded. The profile used in multivariable-adjusted model was: average values for continuous variables, non-smoker, high school education, SBP between 130 and 160, without: diabetes, hormone use and antihypertensive therapy. Women without birth control use. Migr: Migraine, Ctrl: Subjects without migraine, MO: Migraine without aura. MA: Migraine with aura. Migraine defined as answering yes to two of five questions on migraine. (From Paper II).

3.6 Migraine and brain infarcts (III)

The participants were 2693 women and 1996 men, with an average age of 50.9 years (range, 33-65) at the midlife interview and 76.2 years (range, 66-96) at the late-life interview. Infarcts were present on MRI in 39.3% of men and 24.6% of women. The most common lesion location was the cerebellum (21.0% in men and 14.7% in women; see Table 9).

Table 9: Prevalence of Late-Life Infarct-Like Lesion by Midlife Migraine Status: AGES-Reykjavik Study. (From Paper III).

	Infarct Location							
	Cerebellar		Cortical		Subcortical		Total	
	N	Yes	N	Yes	N	Yes	N	Yes
MEN								
No Headache	1589	339 (21.3%)	1573	244 (15.5%)	1573	262 (16.7%)	1589	621 (39.1%)
NMH	294	61 (20.8%)	291	52 (17.9%)	291	42 (14.4%)	294	118 (40.1%)
MO	30	3 (10.0%)	30	7 (23.3%)	30	5 (16.7%)	30	12 (40.0%)
MA	83	16 (19.3%)	83	15 (18.1%)	83	11 (13.3%)	83	34 (41.0%)
Total	1996	419 (21.0%)	1977	318 (16.1%)	1977	320 (16.2%)	1996	785 (39.3%)
WOMEN								
No Headache	1654	240 (14.5%)	1642	131 (8.0%)	1642	138 (8.4%)	1654	415 (25.1%)
NMH	582	66 (11.3%)	578	35 (6.1%)	578	43 (7.4%)	582	125 (21.5%)
MO	179	26 (14.5%)	178	7 (3.9%)	178	10 (5.6%)	179	36 (20.1%)
MA	278	64 (23.0%)	278	23 (8.3%)	278	20 (7.2%)	278	86 (30.9%)
Total	2693	396 (14.7%)	2675	196 (7.3%)	2675	211 (7.9%)	2693	662 (24.6%)

In unadjusted comparisons, infarcts overall were more prevalent in women with migraine with aura than in women without headache (31% vs. 25%; P=0.04; see Table 9), but there was no difference in prevalence for men (41% vs. 39%). Infarcts in the cerebellum, but not in other locations, were more prevalent in women with migraine with aura than in women without headache (23% vs. 15%; P<0.001); there was no difference in prevalence for men (19% vs. 21%). After adjusting for age, sex, and follow-up time in a pooled model for men and women,

participants with midlife migraine with aura were shown at increased risk for total infarcts (adjusted odds ratio [OR], 1.4; 95% CI, 1.1-1.8; Table 10). This mainly reflects the risk associated with lesions located in the cerebellum (adjusted OR, 1.6; 95% CI, 1.3- 2.2; Table 10). There was no increased risk for cortical or subcortical lesions (Table 10) for participants with midlife migraine with aura, migraine without aura, or nonmigraine headache. Results were similar without (model 1) or with (model 2) adjustment for midlife measures of cardiovascular risk. The relationship between migraine with aura and cerebellar infarcts was only significant in women (men, adjusted OR, 1.0; 95% CI, 0.6-1.8 vs. women, adjusted OR, 1.9; 95% CI, 1.4- 2.6; P=0.04 for interaction by sex; see Table 10), but was not statistically different by the age at which headache symptoms were assessed (age <50 years, adjusted OR, 2.0; 95% CI, 1.4- 3.0 vs. age ≥50 years, adjusted OR, 1.4; 95% CI, 0.9-2.0; P=0.18 for interaction by age; see Table 11). For cortical infarcts in the group with migraine without aura, there was interaction by sex, suggesting a higher risk in men than women (P=0.04) although the individual sex-stratified ORs were not significant (Table 11). Results were generally similar when stratified by age (Table 11) although there was also a marginally increased risk for cortical infarcts in participants aged ≥50 years with migraine with aura (adjusted OR, 1.6; 95% CI, 1.0-2.5; P= 0.07).

Secondary analysis results were similar after adjusting for late-life measures of cardiovascular risk and history of CAD or TIA/stroke. The relationship between migraine with aura and cerebellar infarcts was not changed by adjusting for late-life measures of cardiovascular risk and history of CAD or TIA/stroke in the total sample (adjusted OR, 1.5; 95% CI, 1.2- 2.0), or when analyzed separately for men (adjusted OR, 1.0; 95% CI, 0.5- 1.7) and women (adjusted OR, 1.8; 95% CI, 1.3-2.5). The association did not differ by CAD history (interaction, P<0.13) with no CAD history having an adjusted OR of 1.8 (95% CI, 1.2-2.5) and with CAD history having an adjusted OR of 1.2 (95% CI, 0.8-1.9). The relationship did not differ by history of TIA or stroke (no history, adjusted OR, 1.7; 95% CI, 1.2-2.3; vs. with history, adjusted OR, 1.6; 95% CI, 0.8-3.5; P=0.57 for interaction by TIA/stroke history). The separate analyses of visual and sensory aura symptoms suggested that the association of cerebellar infarcts with migraine with aura in women was stronger in those (8.6% of all women) with visual aura (adjusted OR, 2.2; 95% CI, 1.5-3.1) than those (1.7% of all women) with only sensory aura symptoms (adjusted OR, 1.3; 95% CI, 0.6-2.8).

Table 10: Adjusted Odds of Late-Life Infarct-Like Lesions by Mid-Life Migraine Status, Overall and Stratified by Sex: AGES-Reykjavik Study.

	Cerebellar OR (95% CI)		Cortical OR (95% CI)		Subcortical OR (95% CI)		Total Infarcts OR (95% CI)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
TOTAL								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
NMH	0.9 (0.7-1.1)	0.9 (0.7-1.1)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
MO	1.0 (0.7-1.5)	1.0 (0.7-1.5)	0.9 (0.5-1.5)	0.9 (0.5-1.6)	0.8 (0.5-1.4)	0.9 (0.5-1.6)	0.9 (0.7-1.3)	1.0 (0.7-1.4)
MA	**1.6 (1.3-2.2)**	**1.7 (1.3-2.2)**	1.3 (0.9-1.8)	1.3 (0.9-1.9)	0.9 (0.6-1.3)	0.9 (0.6-1.3)	**1.4 (1.1-1.8)**	**1.5 (1.2-1.9)**
MEN								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
NMH	1.0 (0.7-1.4)	1.0 (0.7-1.4)	1.2 (0.9-1.7)	1.3 (0.9-1.8)	0.9 (0.6-1.2)	0.9 (0.6-1.2)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
MO	0.5 (0.1-1.5)	0.5 (0.2-1.7)	1.8 (0.8-4.3)	2.0 (0.8-4.8)	1.1 (0.4-2.9)	1.1 (0.4-2.9)	1.2 (0.6-2.5)	1.3 (0.6-2.7)
MA	1.0 (0.6-1.8)	1.0 (0.6-1.8)	1.3 (0.7-2.4)	1.4 (0.8-2.6)	0.9 (0.4-1.6)	0.8 (0.4-1.6)	1.3 (0.8-2.0)	1.3 (0.8-2.0)
WOMEN								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
NMH	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.8 (0.6-1.2)	0.8 (0.6-1.2)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
MO	1.1 (0.7-1.8)	1.1 (0.7-1.8)	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.8 (0.4-1.5)	0.9 (0.4-1.7)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
MA	**1.9 (1.4-2.6)**	**2.0 (1.4-2.7)**	1.2 (0.7-1.9)	1.2 (0.7-1.9)	0.9 (0.6-1.5)	1.0 (0.6-1.7)	**1.5 (1.1-2.0)**	**1.5 (1.2-2.1)**

Note: Bolded ORs p<0.05. Underlined ORs are significant (p<0.05) interaction by sex for cerebellar and cortical infarcts.
Model 1: Adjusted for age at mid-life examination, sex, and duration of follow-up
Model 2 (includes model 1 adjustments): adjusted for midlife systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index (calculated as weight in kilograms divided by height in meters squared), use of medication for hypertension, smoking history, and diabetes. (From Paper III).

Table 11: Adjusted Odds of Late-Life Infarct-Like Lesions by Mid-Life Migraine Status, Overall and Stratified by Age: AGES-Reykjavik Study.

	Cerebellar OR (95% CI)		Cortical OR (95% CI)		Subcortical OR (95% CI)		Total Infarcts OR (95% CI)	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Age < 50								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1 symptom	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.0 (0.7-1.5)	1.0 (0.7-1.5)	0.9 (0.6-1.3)	0.9 (0.6-1.3)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
2-3 symptoms	1.4 (0.9-2.4)	1.4 (0.8-2.5)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.7 (0.3-1.6)	0.7 (0.3-1.6)	1.2 (0.8-1.9)	1.2 (0.8-1.9)
Visual Aura	**2.0 (1.4-3.0)**	**2.1 (1.4-3.1)**	1.0 (0.6-1.8)	1.1 (0.6-2.1)	0.7 (0.4-1.3)	0.7 (0.4-1.3)	**1.5 (1.1-2.1)**	**1.5 (1.1-2.2)**
Age >= 50								
No Headache	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1 symptom	0.8 (0.6-1.0)	0.8 (0.6-1.0)	1.1 (0.8-1.5)	1.1 (0.8-1.5)	0.9 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.1)	0.9 (0.7-1.2)
2-3 symptoms	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.9 (0.4-2.0)	1.1 (0.5-2.4)	0.7 (0.4-1.2)	0.8 (0.4-1.3)
Visual Aura	1.4 (0.9-2.0)	1.4 (0.9-2.1)	1.6 (1.0-2.5)	**1.6 (1.0-2.6)**	1.1 (0.7-1.9)	1.2 (0.7-2.0)	**1.4 (1.0-2.0)**	**1.5 (1.1-2.1)**

Note: Bolded ORs P≤0.05. ref: reference category. No significant (P<0.05) interaction by age at which headache symptoms were assessed (age <50 vs. ≥50 years).
Model 1: Adjusted for age at midlife examination, sex, and duration of follow-up.
Model 2 (includes model 1 adjustments): adjusted for midlife systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index (calculated as weight in kilograms divided by height in meters squared), use of medication for hypertension, smoking history, and diabetes. (From Paper III).

3.7 Migraine and CV-, non-CV- and all-cause mortality (IV)

There were 9044 men and 9681 women, with an average age of 52.8 years (range: 33 to 81) at study entry. Overall, 10.8% of the participants (6.3% of men; 15.0% of women) were classified as having migraine, including 3.3% migraine without aura (1.4% of men; 5.1% of women) and 7.5% migraine with aura (5.0% of men; 9.9% of women). Of the participants with aura, the proportions with visual aura, sensory aura and both visual and sensory aura, respectively, were 72.1%, 17.4% and 10.5% for men and 64.8%, 16.5% and 18.7% for women. Within the migraine with aura group, 81% of the men and 89% of the women reported having at least one other migraine symptom.

The subjects without headache were significantly older than the subjects with migraine and headache. Systolic BP was lower among men with migraine than men without headache (adjusted for age and use of antihypertensive medication). Pulse pressure was lower among men and women with migraine than subjects without headache. Pulse pressure was lower among men with nonmigraine headache than men without headache (Table 3). Compared to those without headache, subjects with migraine or with MA had less education and were more likely to be on antihypertensive medication and/or on medical hormones.

3.7.1 Migraine and nonmigraine headache (NMH)

Subjects with migraine were at significantly increased risk (hazard ratio, HR and 95% confidence intervals) of all-cause (HR 1.15, 1.08 to 1.23, $p<0.001$) and CV mortality (HR 1.22, 1.10 to 1.36, $p<0.001$), compared with subjects with no headache (Table 2). The risk was similar with and without adjustment for CV risk factors (Table 12). In sex-stratified models, men and women with migraine were at a similarly elevated risk of all-cause mortality (Table 12), interaction by sex P=0.87, but for CV mortality men were at marginally higher risk than women, interaction by sex P=0.057. Women, but not men, with NMH were also at increased risk of CV mortality. The above results were similar when subjects with a history of coronary artery disease (n=266) were excluded from the model.

When CV mortality was divided into CHD, stroke and other CV mortality (Table 13), subjects with migraine were at increased risk of both CHD (sex- and multivariable-adjusted HR 1.22, 1.07 to 1.39, P=0.003) and stroke mortality (HR 1.30, 1.05 to 1.61, P=0.017). However, the risk of CHD and stroke mortality was only significant for men with migraine in the sex-stratified models (Table 13). Men and women with migraine were not at increased risk of other CV mortality.

Table 12: Age- and multivariable-adjusted hazard ratios for all-cause mortality (i) CV mortality (ii) non-CV mortality (iii) according to migraine status in men and women in the Reykjavik Study (n=18 725)*.

Endpoint	Hazard Ratio and (95% Confidence Interval)				
Gender	No				
Adjustment	headache	NMH†	Migraine	MO‡	MA§
(i) All-cause mortality					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=4519	n=845	n=364	n=73	n=291
age-adjusted	1.00	0.99 (0.92 to 1.07)	**1.12 (1.01 to 1.25)**	0.92 (0.73 to 1.17)	**1.19 (1.05 to 1.36)**
mv-adj.ll	1.00	0.99 (0.92 to 1.06)	**1.16 (1.04 to 1.29)**	0.95 (0.76 to 1.20)	**1.23 (1.09 to 1.38)**
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=2958	n=1008	n=664	n=198	n=466
age-adjusted	1.00	1.02 (0.95 to 1.10)	**1.12 (1.03 to 1.22)**	1.00 (0.86 to 1.15)	**1.18 (1.07 to 1.31)**
mv-adj.ll	1.00	1.04 (0.97 to 1.12)	**1.16 (1.07 to 1.26)**	1.06 (0.92 to 1.22)	**1.21 (1.09 to 1.33)**
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=7477	n=1853	n=1028	n=271	n=757
age- & sex-adjusted	1.00	1.01 (0.96 to 1.06)	**1.12 (1.05 to 1.19)**	0.97 (0.86 to 1.09)	**1.18 (1.10 to 1.27)**
mv-adj.ll	1.00	1.01 (0.96 to 1.07)	**1.15 (1.08 to 1.23)**	1.02 (0.91 to 1.16)	**1.21 (1.12 to 1.30)**
(ii) CV-mortality					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=2086	n=388	n=189	n=38	n=151
age-adjusted	1.00	0.99 (0.89 to 1.10)	**1.28 (1.11 to 1.49)**	1.07 (0.78 to 1.48)	**1.35 (1.15 to 1.60)**
mv-adj.¶	1.00	0.97 (0.87 to 1.08)	**1.35 (1.17 to 1.57)**	1.14 (0.83 to 1.57)	**1.42 (1.20 to 1.68)**
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=1061	n=377	n=222	n=66	n=156
age-adjusted	1.00	1.12 (1.00 to 1.26)	1.15 (0.99 to 1.33)	1.04 (0.81 to 1.34)	**1.20 (1.01 to 1.42)**
mv-adj.¶	1.00	**1.13 (1.01 to 1.27)**	1.16 (1.00 to 1.34)	1.09 (0.85 to 1.40)	1.18 (1.00 to 1.40)
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=3147	n=765	n=411	n=104	n=307
age- & sex-adjusted	1.00	1.04 (0.96 to 1.13)	**1.19 (1.07 to 1.32)**	1.02 (0.84 to 1.24)	**1.25 (1.11 to 1.41)**
mv-adj.¶	1.00	1.04 (0.96 to 1.13)	**1.22 (1.10 to 1.36)**	1.10 (0.91 to 1.34)	**1.27 (1.13 to 1.43)**
(iii) non-CV mortality**					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=2433	n=457	n=175	n=35	n=140
age-adjusted	1.00	0.99 (0.90 to 1.09)	0.99 (0.85 to 1.15)	0.81 (0.58 to 1.13)	1.05 (0.88 to 1.24)
mv-adj.ll	1.00	0.98 (0.89 to 1.09)	1.00 (0.86 to 1.17)	0.83 (0.59 to 1.16)	1.05 (0.89 to 1.25)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=1897	n=631	n=442	n=132	n=310
age-adjusted	1.00	0.97 (0.88 to 1.06)	1.11 (1.00 to 1.23)	0.97 (0.81 to 1.16)	**1.17 (1.04 to 1.32)**
mv-adj.ll	1.00	0.99 (0.90 to 1.08)	**1.14 (1.02 to 1.26)**	1.02 (0.86 to 1.22)	**1.19 (1.06 to 1.35)**
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=4330	n=1088	n=617	n=167	n=450
age- & sex-adjusted	1.00	0.98 (0.91 to 1.05)	1.07 (0.98 to 1.17)	0.93 (0.80 to 1.09)	**1.13 (1.03 to 1.25)**
mv-adj.ll	1.00	0.99 (0.92 to 1.05)	**1.10 (1.01 to 1.19)**	0.97 (0.83 to 1.14)	**1.15 (1.04 to 1.27)**

* The number of subjects was originally 18 903, but 68 (0.36%) were lost to follow-up, and 110 (0.58%) were missing data on blood pressure, cholesterol or body mass index; n=18 725 and in all 470 990 years of follow-up.
† NMH: nonmigraine headache, headache without or with one migrainous symptom once or more times per month.
‡ MO: migraine without aura, 2-3 of unilateral, photophobia, nausea symptoms.
§ MA: migraine with visual and/or sensory symptoms. If subjects have MO symptoms and MA symptoms, then classified as MA.
ǁ multivariable-adjusted: age, body mass index, smoking (no, current, previous), education (primary, secondary, college-university), systolic and diastolic blood pressure and antihypertensive medical use.
¶ multivariable adjusted: age, body mass index, smoking (no, current, previous), education (primary, secondary, college-university), SBP, DBP, antihypertensive medical use, cholesterol, diabetes, history of coronary artery disease and birth control use for women.
** non-CV mortality: mortality from causes other than cardiovascular disease.
Bolded values are statistically significant (p<0.05). (From Paper IV).

Table 13: Risk of CV mortality split up into CHD- (i) stroke- (ii) and other CV mortality (iii) according to migraine status in men and women in the Reykjavik Study*.

Endpoint	Hazard Ratio and (95% Confidence Interval)				
Gender	No				
Adjustment	headache	NMH†	Migraine	MO‡	MA§
(i) CHD mortality**					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=1473	n=275	n=136	n=26	n=110
age-adjusted	1.00	0.99 (0.87 to 1.12)	**1.29 (1.08 to 1.54)**	1.03 (0.70 to 1.52)	**1.38 (1.13 to 1.67)**
mv-adj.ll	1.00	0.96 (0.85 to 1.10)	**1.36 (1.14 to 1.62)**	1.12 (0.76 to 1.65)	**1.43 (1.18 to 1.74)**
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=590	n=213	n=123	n=35	n=88
age-adjusted	1.00	1.13 (0.96 to 1.32)	1.13 (0.93 to 1.37)	0.98 (0.69 to 1.38)	1.20 (0.96 to 1.51)
mv-adj.ll	1.00	1.14 (0.98 to 1.34)	1.13 (0.93 to 1.37)	1.03 (0.73 to 1.46)	1.17 (0.93 to 1.47)
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=2063	n=488	n=259	n=61	n=198
age- & sex-adj.	1.00	1.04 (0.94 to 1.14)	**1.19 (1.04 to 1.35)**	0.97 (0.75 to 1.25)	**1.28 (1.10 to 1.48)**
mv-adj.ll	1.00	1.03 (0.94 to 1.14)	**1.22 (1.07 to 1.39)**	1.05 (0.82 to 1.37)	**1.28 (1.11 to 1.49)**
(ii) Stroke mortality ††					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=373	n=63	n=37	n=6	n=31
age-adjusted	1.00	0.92 (0.70 to 1.20)	**1.46 (1.04 to 2.05)**	0.97 (0.43 to 2.18)	**1.62 (1.12 to 2.34)**
mv-adj.¶	1.00	0.90 (0.69 to 1.18)	**1.55 (1.10 to 2.18)**	0.96 (0.43 to 2.15)	**1.76 (1.22 to 2.54)**
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=292	n=99	n=63	n=18	n=45
age-adjusted	1.00	1.08 (0.86 to 1.36)	1.20 (0.91 to 1.58)	1.05 (0.65 to 1.69)	1.27 (0.92 to 1.74)
mv-adj.¶	1.00	1.08 (0.86 to 1.36)	1.20 (0.91 to 1.59)	1.08 (0.67 to 1.75)	1.26 (0.92 to 1.73)
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=665	n=162	n=100	n=24	n=76
age- & sex-adj.	1.00	1.01 (0.85 to 1.20)	**1.27 (1.03 to 1.58)**	1.01 (0.67 to 1.53)	**1.38 (1.09 to 1.76)**
mv-adj.¶	1.00	1.00 (0.84 to 1.19)	**1.30 (1.05 to 1.61)**	1.06 (0.70 to 1.60)	**1.40 (1.10 to 1.78)**
(iii) Other CV mortality**					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=240	n=50	n=16	n=6	n=10
age-adjusted	1.00	1.14 (0.84 to 1.54)	0.97 (0.58 to 1.60)	1.46 (0.65 to 3.29)	0.80 (0.43 to 1.51)
mv-adj.¶	1.00	1.12 (0.83 to 1.53)	1.04 (0.63 to 1.73)	1.54 (0.68 to 3.47)	0.87 (0.46 to 1.64)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=179	n=65	n=36	n=13	n=23
age-adjusted	1.00	1.19 (0.89 to 1.58)	1.16 (0.81 to 1.67)	1.29 (0.73 to 2.28)	1.10 (0.71 to 1.71)
mv-adj.¶	1.00	1.21 (0.91 to 1.61)	1.20 (0.83 to 1.72)	1.33 (0.75 to 2.35)	1.13 (0.73 to 1.76)
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=419	n=115	n=52	n=19	n=33
age- & sex-adj.	1.00	1.15 (0.93 to 1.42)	1.06 (0.79 to 1.42)	1.29 (0.81 to 2.05)	0.97 (0.68 to 1.38)
mv-adj.¶	1.00	1.15 (0.93 to 1.42)	1.12 (0.83 to 1.50)	1.39 (0.87 to 2.21)	1.00 (0.70 to 1.43)

* The number of subjects was originally 18 903, but 68 (0.36%) were lost to follow-up and 110 (0.58%) were missing data on blood pressure, cholesterol or body mass index, n=18 725 and in all 470 990 years of follow-up.
† NMH: nonmigraine headache, headache without or with one migrainous symptom once or more times per month.
‡ MO: migraine without aura, 2-3 of unilateral, photophobia, nausea symptoms.
§ MA: migraine with visual and/or sensory symptoms. If subjects have MO symptoms and MA symptoms, then classified as MA.
ll multivariable-adjusted: age, body mass index, smoking (no, current, previous), education (primary, secondary, college-university), systolic and diastolic blood pressure and antihypertensive medical use.
¶ multivariable adjusted: age, body mass index, smoking (no, current, previous), education (primary, secondary, college-university), SBP, DBP, antihypertensive medical use, cholesterol, diabetes, history of coronary artery disease and birth control use for women.
** CHD: coronary heart disease. non-CHD CV: CV disease other than CHD (stroke and CV disease other than CHD and stroke). Bolded values are statistically significant (p<0.05). (From Paper IV).

3.7.2 MA and MO

Among migraine sufferers, subjects with MA were at increased risk of all-cause and CV mortality (Table 12), but no increased risk was seen in subjects with MO. The long-term effects of migraine on CV mortality were studied using cumulative hazard curves, and it can be seen that men with MA were at marginally higher risk than women with MA (Figure 10); this is also reflected in Table 12, but this difference was marginally significant P=0.053 for interaction by sex. Still, women with MA were at marginally significantly increased risk of CV mortality, compared with women with no headache (HR 1.18, 1.00 to 1.40, P=0.053). The increased risk of CV mortality in subjects with MA was higher among men than women for CHD and stroke mortality, although not significantly; hazard ratios 1.43 in men vs. 1.17 in women for CHD mortality and hazard ratios 1.76 in men vs. 1.26 in women for stroke mortality, P=0.12 and 0.15 for interaction by sex for CHD and stroke mortality (Table 13).

Women with MA were at increased risk of non-CV mortality (HR 1.19, 1.06 to 1.35, P=0.004). To investigate this finding further, non-CV mortality was divided into cancer and non-cancer mortality. Women with MA were not at increased risk of cancer but of mortality other than cancer (HR 1.33, 1.13 to 1.57, P=0.001) (Table 14).

Overall, using total mortality, our model suggests that at age 50 men/women with MA had a median loss of 1.5/1.4 years of life, compared with those without headache (Table 15).

At age 50 the absolute risk of all-cause mortality was low but still considerably higher for men than women. For example, the 10-year risk of mortality for men aged 50 with no headache and MA was 6.8% and 8.0%, respectively; the corresponding values for women were 3.0% and 3.6%. At age 70 the absolute 10-year risk for both men and women had risen to 40.6% and 46.1% for men with no headache and MA, respectively, and to 24.1% and 27.9% for the corresponding groups of women (Table 16).

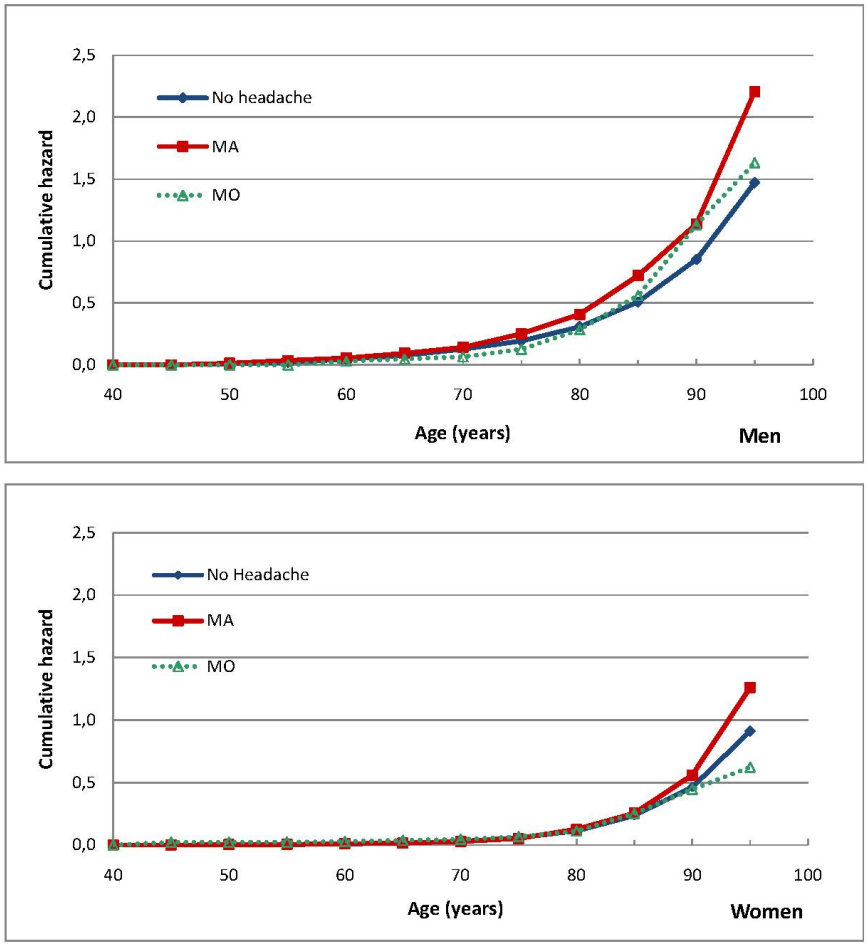

Figure 10: Migraine status and Nelson-Aalen cumulative hazard for CV mortality, the Reykjavik Study.Total number of subjects (n=18 725). MA: migraine with aura, MO: migraine with no aura. The curve for NMH (nonmigraine headache) was super-imposable with the no-headache curve for both men and women and was therefore omitted. (From Paper IV).

Table 14: Non-CV mortality split into cancer mortality and mortality other than CV or cancer according to migraine status in men and women in the Reykjavik Study*.

Endpoint	Hazard Ratio and (95% Confidence Interval)				
Gender	No				
Adjustment	headache	NMH†	Migraine	MO‡	MA§
Cancer mortality					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=1333	n=238	n=93	n=16	n=77
age-adjusted	1.00	0.93 (0.81 to 1.07)	0.94 (0.76 to 1.16)	0.66 (0.40 to 1.07)	1.03 (0.82 to 1.29)
mv-adj.ll	1.00	0.92 (0.80 to 1.06)	0.94 (0.76 to 1.16)	0.68 (0.41 to 1.11)	1.03 (0.82 to 1.29)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=930	n=306	n=214	n=68	n=146
age-adjusted	1.00	0.92 (0.80 to 1.04)	1.01 (0.87 to 1.18)	0.93 (0.73 to 1.20)	1.06 (0.89 to 1.26)
mv-adj.ll	1.00	0.93 (0.82 to 1.06)	1.04 (0.90 to 1.21)	0.99 (0.77 to 1.26)	1.07 (0.90 to 1.28)
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=2363	n=544	n=307	n=84	n=223
age- & sex-adjusted	1.00	0.93 (0.84 to 1.02)	1.00 (0.88 to 1.13)	0.88 (0.70 to 1.09)	1.05 (0.92 to 1.21)
mv-adj.ll	1.00	0.93 (0.85 to 1.03)	1.02 (0.90 to 1.15)	0.92 (0.74 to 1.14)	1.06 (0.93 to 1.22)
Mortality other than CV or cancer					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Mortality	n=1100	n=219	n=82	n=19	n=63
age-adjusted	1.00	1.07 (0.92 to 1.23)	1.05 (0.84 to 1.32)	1.00 (0.63 to 1.57)	1.07 (0.83 to 1.38)
mv-adj.ll	1.00	1.06 (0.92 to 1.23)	1.07 (0.86 to 1.34)	1.02 (0.65 to 1.61)	1.08 (0.84 to 1.40)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Mortality	n=967	n=325	n=228	n=64	n=164
age-adjusted	1.00	1.03 (0.90 to 1.16)	**1.21 (1.04 to 1.40)**	1.02 (0.79 to 1.31)	**1.30 (1.10 to 1.54)**
mv-adj.ll	1.00	1.05 (0.92 to 1.19)	**1.24 (1.07 to 1.44)**	1.07 (0.83 to 1.37)	**1.33 (1.13 to 1.57)**
Men and women	(n=13071)	(n=3631)	(n=2023)	(n=626)	(n=1397)
Mortality	n=2067	n=544	n=310	n=83	n=227
age- & sex-adjusted	1.00	1.04 (0.94 to 1.14)	**1.15 (1.02 to 1.30)**	1.00 (0.80 to 1.25)	**1.22 (1.07 to 1.41)**
mv-adj.ll	1.00	1.05 (0.95 to 1.15)	**1.19 (1.05 to 1.34)**	1.04 (0.84 to 1.30)	**1.25 (1.09 to 1.43)**

* The number of subjects was originally 18 903, but 68 (0.36%) were lost to follow-up for cause specific mortality and 110 (0.58%) were missing data on blood pressure, cholesterol or body mass index, n=18 725 and in all 470 990 years of follow-up.
† NMH: nonmigraine headache, headache without or with one migrainous symptom once or more times per month.
‡ MO: migraine without aura 2-3 of unilateral, photophobia, nausea symptoms.
§ MA: migraine with visual and/or sensory symptoms. If subjects have MO symptoms and MA symptoms, then classified as MA.
ll multivariable-adjusted: age, body mass index, smoking (no, current, previous), education (primary, secondary, college-university), systolic and diastolic blood pressure and antihypertensive medical use.
Bolded values are statistically significant ($p<0.05$). (From Paper IV).

Table 15: Risk factors for mortality and loss of median life-time in years at age 50, the Reykjavik Study.

Gender	Risk factor	All-cause mortality HR (95% CI)	Loss of median life-time in years
Men			
	smoking >=15 cig. /day*	**3.1 (2.5 to 3.8)**	13
	smoking <15 cig. /day*	**2.4 (1.9 to 3.1)**	9
	T2DM†	**1.6 (1.4 to 1.9)**	5
	SBP>=160 vs. SBP<130‡	**1.5 (1.4 to 1.7)**	5
	NMH§	1.0 (0.9 to 1.1)	0.3
	Migraine	1.1 (1.0 to 1.2)	1.0
	MOǁ	0.9 (0.7 to 1.1)	-1.2
	MA¶	**1.2 (1.0 to 1.3)**	1.5
Women			
	smoking >=15 cig. /day*	**3.7 (3.0 to 4.4)**	9
	smoking <15 cig. /day*	**2.3 (1.9 to 2.8)**	6
	T2DM†	**1.6 (1.4 to 1.9)**	3
	SBP>=160 vs. SBP<130‡	**1.5 (1.4 to 1.6)**	3
	NMH§	1.0 (0.9 to 1.1)	-0.1
	Migraine	1.1 (1.0 to 1.2)	0.9
	MOǁ	1.0 (0.8 to 1.1)	-0.4
	MA¶	**1.2 (1.1 to 1.3)**	1.5

Total number of subjects (n=18 725)
Values are age-adjusted unless otherwise indicated.
* cig.: cigarettes, estimates of HR and median life-time for smoking: 2930 men and 3084 women, age 34-61 years, from the Reykjavik Study with a median follow-up of 26 years.[37]
† T2DM: type two diabetes mellitus, estimates of HR and median life-time for type two diabetes: combined values from the Reykjavik Study and Reykjavik AGES Study. Follow-up in the Reykjavik Study was 20 years and 3.5 years in Reykjavik AGES Study.[36]
‡ Subjects on antihypertensive medication omitted, adjusted for smoking status.
§ NMH: nonmigraine headache, headache without or with one migrainous symptom twelve times or more per year.
ǁ MO: migraine without aura, 2-3 of unilateral, photophobia, nausea symptoms.
¶MA: migraine with visual and/or sensory symptoms. If subject has MO symptoms and MA symptoms, then classified as MA.
Bolded values are statistically significant (P<0.05). (From Paper IV).

Table 16: Age-adjusted absolute 10-year risk of CV and all-cause mortality according to migraine status.

Endpoint	Absolute 10-year risk (%) and (95% Confidence Interval)				
Gender / Adjustment	**No headache**	**NMH†**	**Migraine**	**MO‡**	**MA§**
All-cause					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Age 50	6.8 (6.3 to 7.3)	6.7 (6.1 to 7.3)	7.6 (6.7 to 8.5)	6.3 (4.8 to 7.7)	8.0 (7.0 to 9.0)
Age 60	17.4 (16.4 to 18.4)	17.3 (15.9 to 18.6)	19.4 (17.3 to 21.4)	16.2 (12.6 to 19.7)	20.3 (18.0 to 22.6)
Age 70	40.6 (38.4 to 42.7)	40.3 (37.4 to 43.2)	44.3 (40.1 to 48.2)	38.2 (30.6 to 45.0)	46.1 (41.5 to 50.4)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Age 50	3.0 (2.8 to 3.3)	3.1 (2.8 to 3.4)	3.4 (3.0 to 3.8)	3.0 (2.5 to 3.5)	3.6 (3.2 to 4.0)
Age 60	8.8 (8.1 to 9.5)	9.0 (8.2 to 9.8)	9.8 (8.8 to 10.8)	8.8 (7.4 to 10.1)	10.3 (9.2 to 11.5)
Age 70	24.1 (22.4 to 25.9)	24.6 (22.5 to 26.7)	26.7 (24.1 to 29.1)	24.0 (20.6 to 27.4)	27.9 (25.0 to 30.7)
CV mortality					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Age 50	3.3 (3.0 to 3.6)	3.3 (2.8 to 3.7)	4.2 (3.5 to 4.9)	3.5 (2.4 to 4.7)	4.4 (3.6 to 5.2)
Age 60	9.3 (8.6 to 10.1)	9.3 (8.2 to 10.4)	11.8 (10.0 to 13.6)	10.0 (6.8 to 13.0)	12.4 (10.3 to 14.4)
Age 70	24.9 (22.8 to 27.0)	24.8 (21.8 to 27.6)	30.8 (26.3 to 35.1)	26.5 (18.5 to 33.6)	32.2 (27.1 to 36.8)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Age 50	0.6 (0.5 to 0.7)	0.6 (0.5 to 0.8)	0.7 (0.5 to 0.8)	0.6 (0.4 to 0.8)	0.7 (0.5 to 0.8)
Age 60	2.4 (2.1 to 2.8)	2.7 (2.3 to 3.1)	2.8 (2.3 to 3.3)	2.5 (1.8 to 3.2)	2.9 (2.3 to 3.5)
Age 70	9.9 (8.6 to 11.3)	11.1 (9.3 to 12.8)	11.4 (9.3 to 13.4)	10.3 (7.6 to 13.0)	11.8 (9.5 to 14.1)

† NMH: nonmigraine headache, headache without or with one migrainous symptom once or more times per month.
‡ MO: migraine without aura 2-3 of unilateral, photophobia, nausea symptoms.
§ MA: migraine with visual and/or sensory symptoms. If subjects have MO symptoms and MA symptoms, then classified as MA. (From Paper IV).

4 DISCUSSION

4.1 Migraine diagnosis

The one-year prevalence of migraine for men and women was 5.7% and 16.4%, respectively, which is similar to what has been described for western countries, about 6% for men and 15-18% for women (63, 119, 120).

The age distribution for the one-year age- and sex-specific prevalence of migraine in the current study was similar to what has been described by others (51, 119); see Figure 11 for comparison. The average one-year prevalence and age distribution found in the present study gives some assurance that the sample is mainly composed of migraine subjects.

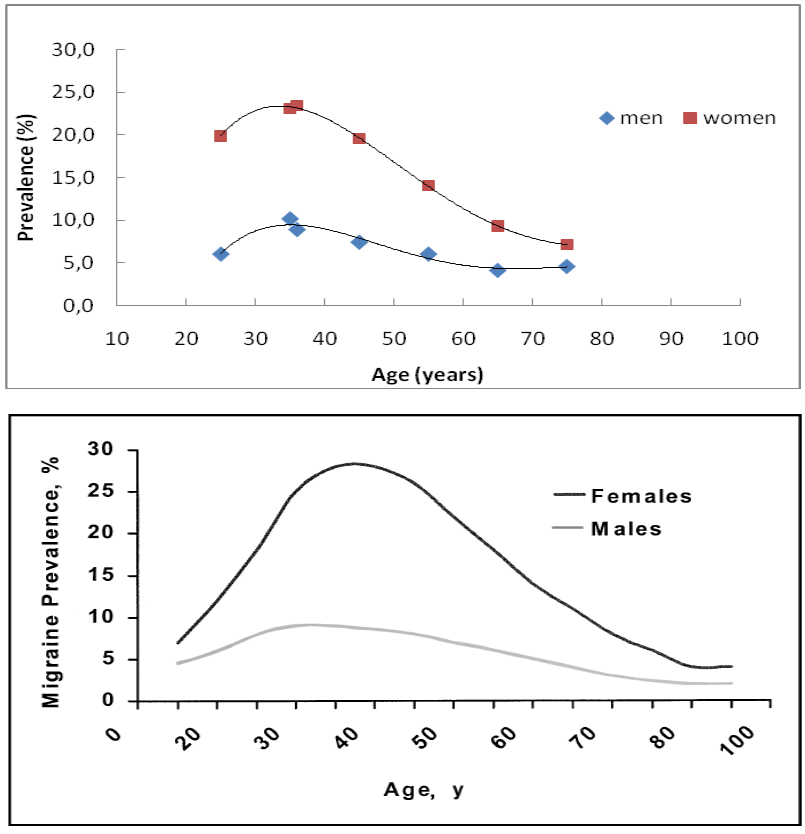

Figure 11: Comparison of age- & sex-specific prevalence of migraine, Fig. 7 and Fig. 4.

Figure 7: Age- and sex- specific one-year prevalence of migraine in the Reykjavik Study and Reykjavik Study for the Young. Prevalence of migraine, defined by a modified version of the 2004 IHS criteria. For both men and women, the first two data points are from Reykjavik Study for the Young (n=2781), and the next five data points are from the Reykjavik Study (n=18 725).

Figure 4: Adjusted age-specific prevalence of migraine by sex. From "Prevalence and burden of migraine in the United States: data from the American Migraine Study II" by Lipton et al. (51)

Preliminary results from a study of 2000 randomly selected Icelanders, using IHS criteria, showed a 7% and 19% prevalence of migraine for men and women, respectively (121), which is similar to the prevalence in the Reykjavik Study when using the loose IHS criteria.

4.2 Further support for using the modified IHS criteria when identifying migraineurs

In a study of 500 migraine patients by Raskin et al., the prevalence of migraine symptoms is shown below (122) (see Table 17). It can be seen that although there are few questions in the Reykjavik Study on migraine symptoms, they cover the most common migraine symptoms.

Another point supporting the effectiveness of the questions in the Reykjavik Study in identifying migraineurs among study participants is the odds of having migraine according to the Gold Standard Diagnosis applied to answers to the Reykjavik Study questions (see Table 17).

Table 17: Migraine symptoms among migraineurs from "Symptoms Accompanying Severe Migraine Attacks in Group of 500 Patients"*.

Symptom	Prevalence
1 one-sided pain	87%
2 nausea/ vomiting	56%
3 visual disturbances	36%
4 photophobia	82%
5 numbness	not available

* in Raskin NH, et al. Harrison's Principles of Internal Medicine, 15th Edition. 2001 (123).

From Figure 12 it can be seen that nausea, disability and photophobia are the best predictors of having migraine. Two of the three best predictors are among the symptoms asked about in the Reykjavik Study (nausea and photophobia).

Figure 7: Age- and sex- specific one-year prevalence of migraine in the Reykjavik Study and Reykjavik Study for the Young. Prevalence of migraine, defined by a modified version of the 2004 IHS criteria. For both men and women, the first two data points are from Reykjavik Study for the Young (n=2781), and the next five data points are from the Reykjavik Study (n=18 725).

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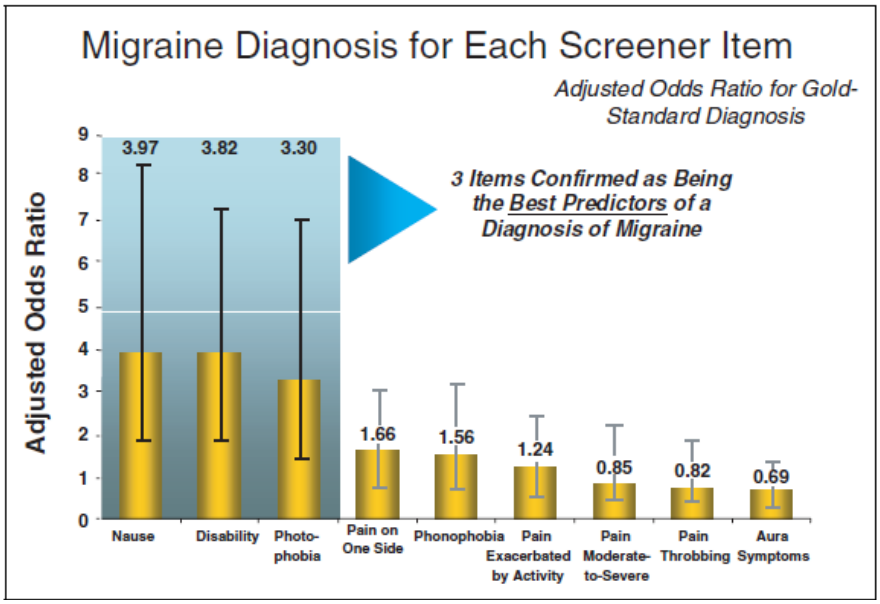

Figure 12: Adjusted odds of a diagnosis of migraine, given that a headache feature is present. (From: Lipton et al., Headache 2007 (124)).

4.3 Prevalence of migraine with and without aura (MA and MO)

In the present study migraine aura symptoms were more prevalent than expected, relative to migraine without aura symptoms (Table 4). Previous results suggest the proportion of migraineurs with aura symptoms to be 31% (78). A population-based study in The Netherlands (GEM, Genetic Epidemiology of Migraine Study) of 6491 adults, aged 20 to 65, reported the one-year prevalence of migraine to be 25% for women and 7.5% for men (57). By combining MA and migraineurs both with and without aura in the GEM Study, the prevalence of MA, MO and unspecified migraine would be 7.5%, 16% and 1.3%, respectively, for women and 2.3%, 4.8%, and 0.4% for men. In the present study the prevalence of MA and MO for women was 8.8% and 5.5%, and the prevalence for men was 3.6% and 1.3%. Comparing the prevalence in the Reykjavik Study and the GEM studies suggests that the prevalence of MA in the Reykjavik Study is consistent with prior results, but the prevalence of MO may be underrepresented. One possible explanation could be recall bias when asked about headache symptoms, especially among milder migraine cases. This has been postulated by Liew G et al., where a higher lifetime prevalence of MA than MO was found among migraineurs in a population-based study of older men and women (102).

4.4 Hypertension and migraine (I)

This study showed no clear association between hypertension and migraine. Similar findings have been reported by others (79-81, 125). There was no association between migraine and diastolic hypertension, but a negative association with systolic hypertension was found among women but not men (100). In 1988 the IHS published a new definition of migraine (40). Most studies on the association between hypertension and migraine were published before that date. Recently, two studies showed a negative association between migraine and hypertension. One found a negative association for both systolic and diastolic hypertension (84), but when adjusting for sex and confounding factors, the association was marginally significant. The other found a negative association with migraine to be similar whether SBP ≥140/DBP ≥90 mmHg or SBP ≥160/DBP ≥95 mmHg was used as the definition of hypertension (85).

The reason for using 160/95 mmHg as a detection limit for hypertension in the Reykjavik Study is that prior to 1980 this was considered to be the upper limit of normal blood pressure (126, 127); by then a majority of the participants of the Reykjavik Study had been examined. Even in 1988 a SBP of 140-159 mmHg was considered "Borderline isolated systolic hypertension" (128).

Since publication of our results, two large studies have been published. Tronvik et al. published data from two large Norwegian population-based studies. The Nord-Trøndelag Health Study, HUNT-1 and HUNT-2 did not show an association between migraine and hypertension, the authors suggest that the introduction of beta blockers in migraine prophylactic treatment may be the reason for reports of headache being more common among individuals with high blood pressure (129).

Bigal et al. published a large case-control study with 6102 migraineurs and 5243 controls representative of the US population and found that migraineurs were more likely to have medical diagnoses of hypertension (33.1 vs. 27.5%, OR 1.4, 95% CI 1.3-1.6) (130) Differences in these results may be due to different definitions of migraine, hypertension and differences between populations and environmental factors.

4.5 Blood pressure and migraine (II)

There was good consistency in the results under loose and strict IHS criteria of migraine and blood pressure and between men and women (Tables 6 and 7). When SBP or DBP was entered into the model, SBP was significantly negatively

associated with migraine, and DBP was not associated with migraine. This is in line with one recent study (85). But when entered jointly, DBP became positively associated with migraine, and it gave significantly lower deviance, thus indicating it was a better model. When SBP and DBP were entered jointly into the regression model, increase in SBP could be seen when DBP was kept constant and vice versa. A positive association between DBP and migraine has been described before, but these studies did not report an inverse association between SBP and migraine (80, 86). An inverse association between SBP and migraine has recently been reported (84, 85), and in the first study there was also an inverse association between DBP and migraine (BP was defined as optimal normal, SBP <130 and DBP <85 mmHg, vs. high or above) (84), but in the second study the inverse association found between DBP and migraine was not significant (85). SBP being negatively associated, and DBP being positively associated with migraine in the present study can possibly explain why many studies show no association between hypertension and migraine (79-81, 125). When an individual has systolic and diastolic hypertension, the possible individual effect of SBP and DBP on migraine (an elevation in SBP associated with decreased probability of having migraine and an elevation in DBP associated with increased probability of having migraine) would cancel each other out. When comparing the deviance of different regression models, it could be seen that SBP had a stronger association with migraine than DBP.

Pulse pressure was negatively associated with migraine for both men and women, and to our knowledge this is the second study describing such an association. The first study (85) could not stratify by sex and did not adjust for antihypertensive medication use. It seems likely that the main connection between BP and migraine is through inverse association between SBP and migraine, because when adjusting for antihypertensive medication, systolic hypertension was negatively associated with migraine, but diastolic hypertension was not. This, together with the results for the regression model excluding subjects on antihypertensive medication, further supports that SBP has a stronger association with migraine than DBP.

Since our publication data from the Norwegian HUNT studies have also shown PP to be inversely associated with migraine, and the association was less clear in subjects using antihypertensive medication (129). The Norwegian study allowed prospective study of the association and found that increasing PP was protective for migraine.

4.5.1 Possible mechanism

The pathophysiological mechanisms behind migraine are poorly understood, and although mechanistic explanations of the association between migraine and blood pressure are not available, some possibilities have emerged. There is some evidence of the involvement of calcitonin gene-related peptide (CGRP) in migraine (131). It has been found that the basal CGRP concentration in blood is higher in migraine patients than healthy controls (132), intravenous administration of CGRP can trigger a migraine attack (133), and a CGRP receptor antagonist has been developed and shown to be effective in the treatment of acute migraine attacks (131, 134), but their safety as preventive medication for migraine is currently being evaluated (135, 136). As CGRP is a potent vasodilator (137), it seems possible that its involvement in migraine could explain some of the findings in the present study.

Another possible mechanism is the involvement of serotonin (5-HT). Platelet serotonin has been found to be lower in migraineurs than in matched controls (138). Serotonin is mainly a vasoconstrictor, which could also explain some of the findings of the present study.

A plausible explanation of our results is a phenomenon called hypertension-associated hypalgesia, which is a diminished sensation of pain resulting from a raised pain threshold. Both animal and human studies have shown that stimulation of the baroreflex arch due to increased BP may inhibit pain transmission at both spinal and supraspinal levels, possibly due to an interaction of the centres modulating nociception (perception of a painful stimulus) and cardiovascular reflexes in the brainstem (129, 139-142). The current study consistently showed PP to be negatively associated with migraine. PP increases with age, and it is related to arterial wall stiffness. It is known that increased PP in healthy middle-aged subjects is associated with reduced baroreflex sensitivity (143).

4.6 Migraine and C-reactive protein (CRP), (II)

In this nested case-control study, age-specific analysis of serum CRP levels was performed in subjects from two large cohort studies. Differences in CRP values between migraineurs and those without migraine were not significant, whether using linear regression with log-transformed CRP levels as a continuous variable or logistic regression with CRP as a binary variable. There was a moderate negative association between CRP levels and age among women with migraine without aura.

Inflammatory mechanisms have been involved in recent years and conceptualized in the neurogenic inflammation theory postulated by Moskowitz and co-workers (144).

This theory accounts for the clinical efficacy of NSAIDs and other anti-inflammatory drugs in aborting migraine attacks. Furthermore, inflammation being an important factor in atherogenesis and atherothrombosis, the association of migraine, especially migraine with aura, with stroke could be based on vascular inflammation as a link. The inference that inflammation is an important component in subsets of migraineurs has been further supported by the recent findings that the inflammatory marker, CRP, may be elevated in migraineurs (88, 90, 91). However, in all of these studies, the elevation of CRP was modest at most and restricted to migraineurs without aura, a group that has not been generally found to be at increased risk of stroke (70, 94, 145). The principal finding of the present study is that CRP levels were not elevated among migraine sufferers compared with nonmigraineurs. Nonetheless, certain subtleties require further consideration.

The multivariable-adjusted values in the Reykjavik Study were fairly low because they reflected subjects with a low cardiovascular disease risk profile. Age-adjusted CRP levels among men with migraine without aura were borderline lower than the levels of nonmigraineurs and also borderline lower than the levels of migraineurs with aura, but after multivariate adjustment, the differences between these groups were smaller and not statistically significant. CRP levels among migraineurs with aura and nonmigraineurs were similar in all age categories for both men and women.

The association between migraine status, CRP and age seemed to be more complex in women than in men. Women with migraine without aura had slightly higher multivariable-adjusted CRP values in the age group 19 to 34 years. With increasing age the CRP level for women without aura fell and became significantly lower than that of nonmigraineurs in the age group 60 to 81 years. Results for women in the age group 19 to 34 years are similar to those published by Vanmolkot et al. (90). In their study 78% of the participants were women, and the mean age was 25 years. The median CRP of those with migraine without aura was 2.11 mg/l, compared with 0.90 mg/l in controls, P=0.0002. In a cohort study of women (mean age 55 years), the multivariable-adjusted prevalence odds ratio of having CRP >4.2 mg/l was 1.14 (95% CI: 1.02-1.27) for active migraine without aura and 1.10 (95% CI: 0.97-1.26) for active migraine with aura vs. 1.00 for no history of migraine as a control (91). That cohort study also showed a slight positive association between the attack frequency and the odds of having elevated CRP (91). While it is clearly established that the prevalence of migraine is lower in older adults than middle-aged adults, it is not clear whether average attack frequency decreases with age. For example, Bigal et al. showed that the proportion of migraineurs with 10 to 14 headache days per month increased with age, and the attacks were less typical in elderly individuals (146), and

Prencipe et al. show a similar attack frequency with increasing age among elderly migraineurs (147). In light of the current knowledge on changes in attack frequency with age, it is not evident what effect age could have on CRP values among different age groups of migraineurs. Headache frequency was not estimated in the Reykjavik Study, so this question cannot be addressed.

In the present study, although not statistically significant, multivariable-adjusted CRP levels were generally higher in migraineurs with aura then migraineurs without aura, and this contradicts the results in the retrospective study of Welch and co-workers (88), the case control study of Vanmolkot et al. (90) and the cohort study of Kurth et al. (91).

The data in the current analysis from the Reykjavik Study were selected on the basis of the availability of CRP measurements. The CRP measurements were part of a nested case-control study, thus raising the possibility of selection bias. However, we note that the age-specific prevalence of migraine in the sub-cohort used was almost identical to the prevalence within the entire cohort, which was randomly selected. This suggests that selection bias with regard to the presence of migraine is not more prevalent in the sub-cohort than in the entire cohort of over 21 000 subjects (100). Due to the selection criteria, there is probably an over-representation of cases with pre-existing coronary heart disease in the current study. When those who did not have a major coronary event during follow-up were analyzed separately, the CRP values were similar to the ones based on all cases. This indicates that the association between CRP values and migraine status is not different among subjects with coronary heart disease.

The questions in our study covered the most common migraine symptoms but did not include all of those identified in the 1988 IHS criteria (40). This is a cross-sectional analysis and cannot account for within-individual changes in CRP values. Furthermore, cross-sectional analysis cannot be used to determine any temporal relationship between CRP levels and the onset of migraine. The subjects entered the study from 1967 to 1991, resulting in a long period of sampling and analysis. However, a study of CRP and cardiovascular disease in subjects from the Reykjavik Study showed that the decade-to-decade consistency of CRP values was good (148). Alcohol use was not measured in the current study. Migraineurs have been reported to be less likely to consume alcohol than nonmigraineurs (78), and alcohol is associated with a decrease in CRP levels (149, 150). Therefore, alcohol use is a potential confounder that cannot be adjusted for in the current study.

In the present study, contraceptive use among women resulted in a two- to three-fold increase in CRP values (data not shown). Frölich et al. found that CRP level among 844 women, in the MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Augsburg survey, aged 25 to 44 years, was 0.81 mg/l among non-users of oral contraceptives and 2.59 mg/l among oral contraceptive users (112). Our results for women without migraine are similar when multivariable adjustment (including oral contraceptive use) was applied (Tables 2 and 4).

There is also potential misclassification of MO subjects as MA subjects, as some MO subjects experience non-specific visual disturbances during headaches, and the questions used do not distinguish between visual disturbances during the pain and before it starts. The effect of this misclassification might have been to attenuate or obscure possible differences in CRP levels between migraineurs with and without aura.

The questions on migraine symptoms in the Reykjavik Study did not allow for identifying subjects with cluster headache (symptoms: one-sided headache and in some cases nausea, sensitivity to light and aura), and these subjects were most likely included with the migraineurs. Two studies by Remahl et al. did not show a difference in CRP values between subjects with cluster headache and subjects without headache, but these studies had few subjects (27 and 21 cases of cluster headache) and thus lack the power to detect small differences (151, 152). The estimated lifetime prevalence of cluster headache is less than 0.3% (111) and is therefore unlikely to affect our results to a great extent.

Information on the use of aspirin and statins was not recorded in this study, and both drugs can alter CRP values. However, we note that the use of these drugs was uncommon in the general population of Reykjavik between 1967 and 1991.

Migraine attacks have considerable effects on the daily lives of migraine sufferers. A survey by the World Health Organization (WHO) rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders. This ranking suggests that in the judgment of the WHO, a day with severe migraine is as disabling as a day with quadriplegia (153).

In a cross-sectional population-based epidemiological survey of headache in Denmark, of those gainfully employed participants with migraine in the previous year, 43% (29/67) said they had been absent from work at least once during the year because of migraine (154). A recent prospective cohort study examined the risk of absence because of sickness among 27 127 female public-sector

employees by migraine status. Migraine was related to 5.4 extra sickness absence days per person-year (155). From the above it can be assumed that those with the most severe migraine are unlikely to attend a voluntary visit to a research clinic during a migraine attack and would be more likely to attend when the attack had subsided. If we assume subjects attending the Reykjavik Study are not having a migraine attack during their visit (migraineurs assumed interictal), we can say that CRP values are not elevated between migraine attacks; therefore, CRP elevation during migraine attack cannot be ruled out. A search of the literature did not reveal studies measuring CRP levels during migraine attacks.

4.6.1 CRP's possible effects on risk among migraineurs of developing CHD

Findings for subjects developing a coronary event during follow-up were similar. The difference in multivariable-adjusted CRP values after excluding those who were later diagnosed with MI ranged from zero to 0.15 mg/l lower (0% to 19% decrease) for men and from 0.14 mg/l higher to 0.05 mg/l lower (23% increase to 8% decrease) for women (see Table 18). This comparison indicates that the association between CRP and development of CHD is similar in subjects with and without migraine.

4.7 Migraine and brain infarcts (III)

In a large cohort of Icelandic adults, we found that women reporting migraine with aura in middle age were at increased risk of late-life infarcts, relative to those without migraine symptoms. The risk was primarily for cerebellar lesions; there was no increased risk for cortical or subcortical lesions in these women or for those with migraine without aura or nonmigraine headache. This risk was independent of the cardiovascular risk factors measured in midlife or late life. Risk was not statistically different between individuals aged 50 or younger vs. those who were older when headache was ascertained or between those with a history of diagnosed CAD or TIA/stroke vs. those with no history.

Table 18: Age- and multivariable-adjusted CRP values and migraine status for men (i) and women (ii) without major coronary event during follow-up, the Reykjavik Study and Reykjavik Study for the Young.

i) Men

Cohort	Average age and range	Migraine status	n	Age-adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl	Multivariable-adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl
Reykjavik	27	Control	513	0.58 (0.53, 0.63)				0.60 (0.48, 0.74)			
young	19-34	Migraine	32	0.61 (0.43, 0.88)	P=0.74			0.61 (0.41, 0.92)	P=0.89		
		MO	13	0.50 (0.29, 0.88)		P=0.36	P=0.63	0.50 (0.28, 0.90)		P=0.32	P=0.51
		MA	19	0.70 (0.44, 1.12)				0.71 (0.43, 1.19)			
Reykjavik	44	Control	763	1.01 (0.94, 1.09)				0.67 (0.56, 0.80)			
	35-49	Migraine	39	1.01 (0.75, 1.38)	P=0.98			0.66 (0.47, 0.94)	P=0.96		
		MO	9	1.02 (0.54, 1.94)		P=0.98	P=0.97	0.61 (0.32, 1.18)		P=0.78	P=0.77
		MA	30	1.01 (0.71, 1.44)				0.68 (0.46, 1.00)			
Reykjavik	54	Control	1231	1.17 (1.11, 1.23)				0.74 (0.66, 0.84)			
	50-59	Migraine	72	1.00 (0.80, 1.26)	P=0.20			0.69 (0.56, 0.84)	P=0.55		
		MO	27	0.86 (0.60, 1.25)		P=0.31	0.11	0.62 (0.44, 0.87)		P=0.27	P=0.22
		MA	45	1.10 (0.83, 1.46)				0.72 (0.56, 0.92)			
Reykjavik	66	Control	595	1.41 (1.30, 1.52)				1.15 (0.96, 1.39)			
	60-79	Migraine	20	1.43 (0.80, 2.27)	P=0.95			1.24 (0.76, 2.01)	P=0.76		
		MO	3	0.76 (0.26, 2.22)		P=0.20	P=0.26	0.75 (0.26, 2.19)		P=0.30	P=0.43
		MA	13	1.65 (0.99, 2.75)				1.39 (0.82, 2.37)			

ii) Women

Cohort	Average age and range	Migraine status	n	Age-adjusted mg/l CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl	Multivariable-adjusted mg/ CRP (95% CI)	Migr vs. Ctrl	MO vs. MA	MO vs. Ctrl
Reykjavik	27	Control	528	0.78 (0.71, 0.86)				0.78 (0.65, 1.02)			
young	19-34	Migraine	136	0.81 (0.67, 0.97)	P=0.77			0.89 (0.68, 1.16)	P=0.38		
		MO	69	0.92 (0.71, 1.19)		P=0.14	P=0.24	1.02 (0.75, 1.39)		P=0.10	P=0.08
		MA	67	0.70 (0.54, 0.91)				0.77 (0.57, 1.05)			
Reykjavik	44	Control	236	0.85 (0.70, 1.02)				0.71 (0.50, 1.01)			
	35-49	Migraine	40	0.76 (0.53, 1.07)	P=0.56			0.69 (0.45, 1.06)	P=0.90		
		MO	15	0.75 (0.43, 1.32)		P=0.98	P=0.67	0.74 (0.41, 1.32)		P=0.75	P=0.87
		MA	25	0.76 (0.49, 1.17)				0.66 (0.40, 1.09)			
Reykjavik	54	Control	498	1.02 (0.93, 1.12)				0.75 (0.61, 0.91)			
	50-59	Migraine	64	1.03 (0.80, 1.33)	P=0.95			0.80 (0.59, 1.08)	P=0.58		
		MO	21	0.72 (0.46, 1.12)		P=0.05	P=0.13	0.61 (0.39, 0.95)		P=0.11	P=0.33
		MA	43	1.23 (0.90, 1.69)				0.93 (0.66, 1.33)			
Reykjavik	66	Control	377	1.46 (1.32, 1.60)				1.15 (0.90, 1.45)			
	60-81	Migraine	28	1.25 (0.94, 1.70)	P=0.33			0.87 (0.61, 1.25)	P=0.07		
		MO	11	0.87 (0.51, 1.48)		P=0.11	P=0.06	0.55 (0.31, 0.96)		P=0.04	P=0.006
		MA	27	1.45 (1.03, 2.04)				1.06 (0.71, 1.58)			

CRP, migraine status, age and gender in the Reykjavik Study and the Reykjavik Study for the young using linear regression, adjusting for age, BMI, cholesterol, smoking, education, hormone use, diabetes mellitus, SBP and antihypertensive. Each age category was analysed separately and subjects with CRP values >=10 mg/l were excluded. Profile used in multivariable-adjusted model was: average values for continuous variables, non-smoker, high school education, SBP between 130 and 160, without: diabetes, hormone use and antihypertensive therapy. Women without birth control use. Migr: Migraine, Ctrl: Subjects without migraine, MO: Migraine no aura, MA: Migraine and aura. Migraine defined as answering yes to two of five questions on migraine. (Unpublished data from Paper II).

Given the age of our study population, it is worth considering the extent to which overall or cardiovascular-related mortality may have affected our results. In particular, those with migraine with aura have been reported to be at increased risk of cardiovascular death, compared with others (70). If individuals with midlife migraine with aura were more likely to die of cardiovascular disease before the late-life examination, and if these individuals were also more likely to have infarcts in the cerebellum or overall, compared with others, then our results would have been attenuated. However, if these cerebellar or overall lesions were somehow protective (e.g., individuals with migraine with aura, and these lesions had lower all-cause mortality, compared with those with migraine with aura without these lesions), then our results would have been exaggerated. The second scenario seems unlikely. Analyzing CVD mortality in relation to migraine and aura status in the Reykjavik Study supports the first scenario, where men with migraine with aura were at marginally higher risk of CVD mortality (HR 1.35 for MA men and HR 1.16 for MA women, P=0.053 for interaction by sex). Our results are consistent with the cross-sectional CAMERA study (96), the only other study that measured infarcts on MRI with a protocol similar to the AGES-Reykjavik Study, which also found the migraine-associated infarcts to be preferentially located in the cerebellum. Our prospective longitudinal study had a long follow-up and an older cohort with a much higher background risk for brain lesions. Our results suggest that the association of infarcts with migraine with aura is detectable in older individuals who typically have cardiovascular risk factors leading to lesions similar in appearance (156). Furthermore, the study is based on a large sample of men and women; therefore, sex differences could be investigated. We found that the relationship between migraine with aura and cerebellar infarcts may be specific to women. However, we cannot rule out increased risk for men with migraine with aura due to the relatively small number of men with migraine with aura in our sample.

Why migraine, particularly with aura, is associated with clinical and (presumably) silent ischaemic stroke is uncertain. Proposed mechanisms include atherosclerotic and nonatherosclerotic causes, including traditional cardiovascular risk factors, endothelial dysfunction, shared genetic risk factors for migraine and stroke, vasoconstrictor medications taken to treat headache, cardiac abnormalities including patent foramen ovale, and diagnostic artefact (97, 157), among other factors (more detail on mechanisms in chapter 4.10). It has also been suggested that cortical spreading depression, the presumed substrate of migraine aura, may predispose to brain lesions by reducing cerebral

blood flow and by activating a cascade of inflammatory events (158). Recent data from the CAMERA study indicate that iron accumulation in deep-brain nuclei may be involved in the formation of the brain lesions in migraineurs (159). These mechanisms do not obviously explain why infarcts associated with migraine with aura would be preferentially located in the cerebellum and in women. There are clinical reports suggesting that the cerebellum is vulnerable in individuals with migraine (160-163) and in familial hemiplegic migraine — a rare Mendelian variant of migraine with aura (164).

In population studies, no particular location pattern was evident for clinically evident ischaemic stroke among women with aura (93, 145), although as mentioned earlier, silent infarcts (as per the CAMERA study) were preferentially located in the cerebellum (96). We also note that secondary analyses suggested an association between migraine with aura and cortical infarcts in some subgroups was stronger (e.g., men with migraine with or without aura or men and women who were older than aged 50 years at the time of headache assessment).

4.8 Migraine and CVD, non-CVD and all-cause mortality (IV)

In the current study, men and women with migraine were at increased risk of all-cause and CV mortality, compared with those without headache. The risk increase was specific to those with migraine with aura (MA). Men and women with MA were at similarly elevated risk of all-cause mortality, but men with MA were at marginally higher risk of CV mortality than women with MA. Women with MA were also at increased risk of non-CV mortality.

This is the first population-based cohort study to measure all-cause and CV mortality in both men and women with migraine separately by aura status. Our findings are consistent with the increasing evidence that migraine, particularly migraine with aura, is associated with CV disease (69, 70, 89, 130). Previous reports where migraine has been protective for all-cause mortality (68, 71, 101) may be explained by methodological differences from this study. For example, two of these studies (68, 71) were based on patient- rather than population-based samples. Furthermore, one of these studies (71) identified migraine sufferers based in part on their use of triptans – contraindicated in those with risk factors for CV disease (165). It must be mentioned that the aim of the two studies (68, 71) was not to compare risk of migraineurs to nonmigraineurs but to assess possible risk of triptan use in subjects with migraine. The fact that the two (68, 71) studies were protective could also explain why a recent meta-analysis of five studies (including the two studies discussed here above) showed no risk for CV mortality associated with migraine overall (with and without combined

aura) (relative risk 1.03, 0.79 to 1.34) (67). Only one study included in this meta-analysis (70) estimated the risk of mortality separately in migraineurs with aura. This study suggested that women with MA were at roughly doubled risk of cardiovascular mortality, compared with women without headache.

The HR values for CV mortality for men with migraine were somewhat higher than the corresponding values for all-cause mortality. The risk of CV mortality was independent of traditional risk factors for CV disease measured at baseline. Several studies have reported greater risk of stroke in migraineurs than in others (67, 89, 130), especially for those with aura (67, 70, 89, 130), The risk of coronary heart disease among migraineurs varies more between studies, from being protective to being a moderately elevated risk (67). The risk increase for CHD mortality and stroke mortality was mainly confined to subjects with MA in the current study. For example the risk of CHD mortality was HR 1.28 (1.11 to 1.49) for MA and HR 1.05 (0.82 to 1.37) for MO subjects, compared with those with no headache, and the corresponding values for stroke mortality were HR 1.40 (1.10 to 1.78) for MA and HR 1.06 (0.70 to 1.60) for MO subjects.

Women with MA were at increased risk of non-CV mortality which was not due to increased risk of cancer but increased risk of non-CV mortality other than cancer. This is a novel finding requiring confirmation in another cohort. The non-CV non-cancer mortality needs to be further divided into more specific end-points in order to identify the potential reasons for the risk increase seen in the current study. Asthma, hay fever, chronic bronchitis, chronic obstructive pulmonary disease and allergies have been reported as co-morbid conditions associated with migraine (166-168) and are potential candidates in the search for what drives the risk increase. Other potential candidates include epilepsy and depression (169).

4.8.1 Potential misclassification and effect modification

The combination of visual symptoms and headache can be symptoms of a transient ischaemic attack (TIA). If TIA were misclassified as migraine with aura in our study, it might exaggerate the association between migraine and CV mortality. However, our diagnosis of migraine required headache at least once a month during the last 12 months, which is not a feature of TIA. We therefore believe it unlikely that this type of misclassification would have appreciably affected the results reported herein.

Neither data on migraine-specific treatment, such as ergotamine and triptans, nor data on the use of analgesics or medical steroids were available; therefore, the potential

modifying effects of these medications on the association between migraine and CV disease could not be estimated in the current study.

4.8.2 Updated meta-analysis with new data from the Reykjavik Study

Schurks et al. (67) performed a meta-analysis and did not find a difference between those with migraine and those with no migraine; the combined-effect estimate was RR 1.03 (95%CI 0.79-1.34) (Figure 13). The meta-analysis is reanalyzed with data from the Reykjavik Study (Table 19).

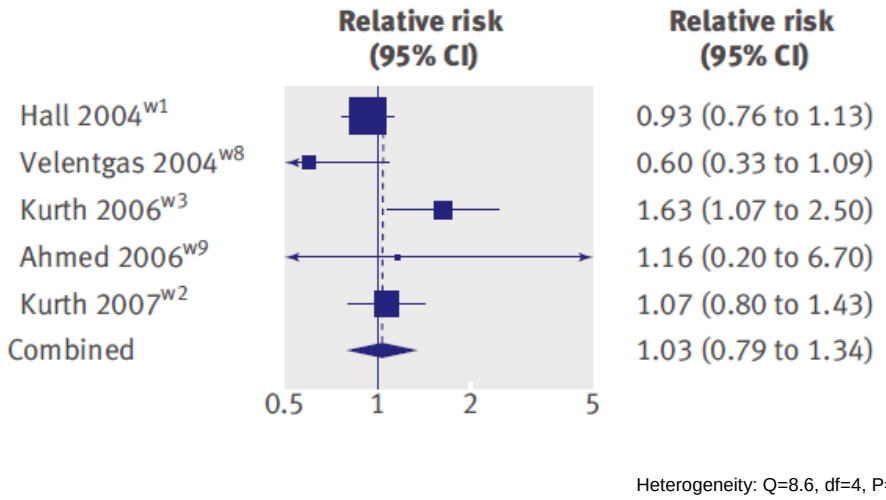

Figure 13: Any migraine type and CVD mortality, meta-analysis. (From Schurks et al., BMJ 2009 (67)).

Table 19 shows that when the case-control studies and cohort studies are combined, there is considerable heterogeneity. The estimated effect for the case-control studies is 0.82, while it is 1.25 and statistically significant for the cohort studies (Table 19). Among the cohort studies men and women had the same risk, both at significantly increased risk. Two studies had information on migraine aura, but when MA women were analysed separately, there was borderline significant heterogeneity, and the confidence interval for the effect size was large.

4.8.3 Possible interaction between migraine and pulse pressure and effects on mortality

When migraine with and without aura and all-cause mortality is examined using age as a time reference, it can be seen that MO subjects have lower (age-adjusted) mortality at middle age, compared with subjects with no headache (Figure 10).

Table 19: Updated meta-analysis for migraine and CVD mortality with new data from the Reykjavik Study.

Any migraine and CVD mortality	No of studies	Relative risk (95% CI)	Heterogeneity Q	Heterogeneity P value
All studies (case-control and cohort)	7	1.13 (0.95-1.34)	16.3	0.01
Case-control studies	2	0.82 (0.56-1.21)	1.9	0.17
Cohort studies	5	1.25 (1.12-1.39)	4.7	0.32
Cohort studies				
Men	2	1.25 (1.00-1.55)	2.0	0.16
Women	3	1.23 (1.02-1.48)	2.2	0.33
Women MA	2	1.54 (0.80-2.94)	3.9	0.05
Women MO	2	1.08 (0.86-1.38)	0.0	0.95

The meta-analysis of Schurks et al. (67) updated with data from the Reykjavik Study.
Studies included in updated meta-analysis, using random effects model.
Case control studies: Hall 2004 (68), Velentgas 2004 (71)
Cohort studies: Kurth 2006 (70), Ahmed 2006 (170), Kurth 2007 (69) Current study entered males and females separately.
Cohort studies men: Kurth 2007, Current study.
Cohort studies women, MA and MO: Kurth 2006, Current study. (Paper IV).

We have previously shown that migraineurs have lower systolic and lower pulse pressure, compared with subjects with no migraine. Therefore we did a Cox regression and introduced PP as an interaction term with migraine aura-/headache-status into a model with men and women, adjusting for age and sex. When smoking, education, SBP, DBP and BMI were added, the interaction between migraine and PP was somewhat attenuated. This indicates that migraineurs without aura have some benefit in reduced all-cause mortality due to lower pulse pressure (borderline significant), compared with subjects with no headache (Table 20).

Table 20: Interaction between headache/migraine status and pulse pressure in relation to all-cause mortality.

	Interaction	HR	95% CI	P-value
Age- and sex-adjusted				
	MA x PP	0.998	(0.994-1.003)	0.49
	MO x PP	0.992	(0.983-1.001)	0.065
	NMH x PP	1.001	(0.998-1.004)	0.34
Multi-var adjusted				
	MA x PP	0.999	(0.994-1.004)	0.68
	MO x PP	0.992	(0.984-1.001)	0.08
	NMH x PP	1.001	(0.998-1.004)	0.56

Cox regression model used Hazard ratio (HR) calculations and 95% confidence intervals.
MA: migraine with visual and/or sensory symptoms. If subject has MO symptoms and MA symptoms, then classified as MA.
MO: migraine without aura, 2-3 of unilateral, photophobia, nausea symptoms. NMH: nonmigraine headache, headache without or with one migrainous symptom twelve times or more per year.
Multi-var adjusted: Age, sex, smoking, education, SBP, DBP and body mass index. (Unpublished data from Paper IV).

4.8.4 The risk of all-cause mortality in context with established risk factors

The increased risk of overall or CV-related mortality associated with MA is significant but modest: 21% for women and 23% for men, with respect to all-cause mortality, and 18% for women and 42% for men, with respect to CV mortality. We estimated that at age 50 men/women with MA had a median loss of 1.5/1.4 years of life, compared with those without headache. By way of comparison to more established risk factors for all-cause mortality, the median loss of life in the Reykjavik Study for those with untreated high blood pressure ≥160 mmHg, type two diabetes, and smoking 15 cigarettes or more per day was, respectively, approximately 5, 5 and 13 years for men and 3, 3 and 9 years for women (171, 172) (Table 15).

4.8.5 The absolute 10-year risk of all-cause mortality

Another way of looking at risk associated with having migraine is to use absolute 10-year risk. When comparing migraineurs with aura to those without headache, the excess absolute 10-year risk of all-cause mortality at age 50 was low: 1.2% for men (8.0% vs. 6.8% risk of all-cause mortality) and 0.6% for women (3.6% vs. 3.0% risk of all-cause mortality). At age 70, the excess absolute risk of all-cause mortality in migraineurs with aura was higher, at 5.5% for men (46.1% vs. 40.6% risk of all-cause mortality) and 3.8% for women (27.9% vs. 24.1% risk of all-cause mortality) (Table 16).

4.9 Are there factors associated with both onset of migraine and CVD?

Heredity plays an important role in migraine (13). Migraine aetiology is complex and involves both multiple genetic and environmental factors (13). Vascular dysfunctions have been suggested a potential link between migraine and increased risk of cardiovascular events (173), and this risk increase has been shown in population-based studies, particularly among migraineurs with aura (70, 174). Pathophysiological mechanisms of atherosclerosis and CVD have been associated with migraine and may explain the increased risk for CVD among people with migraine (173).

Body mass index has been studied in relation to both migraine and CVD. Population-based studies have shown that BMI group was not associated with the prevalence of migraine, but was associated with the frequency of headache attacks. These studies showed that attack frequency, severity, and clinical features of migraine increased with body mass index group (175, 176). A recent population-based study showed an

association between total body obesity, measured by BMI, and migraine among subjects age 20-55 years but not among subjects older than 55 years (177). Numerous studies have shown BMI is associated with risk of CVD. Systemic review of 40 studies with 250 152 patients that had a mean follow-up of 3.8 years showed a U-shaped association between risk of CVD mortality and BMI group (178). Patients with low BMI (that is, <20) had increased relative risk (RR) for total mortality (RR=1.37 [95% CI 1.32-1.43), and cardiovascular mortality (1.45 [1.16-1.81]), compared with patients with normal BMI (range 20-25).

Patients with severe obesity (> or =35) did not have increased total mortality (1.10 [0.87-1.41]), but they had the highest risk for cardiovascular mortality (1.88 [1.05-3.34]) (178).

Stressful events, like a loss of a close relative/spouse, has been associated with new onset of migraine (14). Numerous studies show mental stress as the most prevalent trigger of migraine attacks (7, 21-23), but a cohort study of work stress and new-onset migraine among female employees did not show an association with work-related stress (24). This cohort study showed that high effort-reward imbalance might function as a modifiable risk factor for new-onset migraine.

Several studies have shown an increased cardiovascular risk after earthquakes (179-182), for example, a study of the cardiovascular consequences of the Northridge, California, earthquake in 1994, magnitude 6.7, showed a dramatic increase in CVD deaths on the day of the earthquake, compared with the same date in previous years (RR 2.6, 95% CI 1.8-3.7) (179). There was a 2.3-fold incidence in life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack during the 30-day period following the attack, compared with all other months between May 2001 and October 2002 (183).

The INTER-HEART study (A Global Case-Control Study of Risk Factors for Acute Myocardial Infarction) explored the relation of chronic stressors to the incidence of myocardial infarction in approximately 25 000 subjects from 52 countries (184). Stress either related to work or home that resulted in feeling irritable, filled with anxiety or sleep difficulties resulted in more than a 2.1-fold increase in the risk of developing myocardial infarction. There are also studies showing that a work-related effort-reward imbalance results in increased risk of MI (185, 186).

4.10 Migraine and CVD mechanisms

Several mechanisms may explain the link between migraine and CV disease. Migraine and ischaemic events have been linked through a genetic component (97,

187). They may reflect associations between MA and vasculopathy, such as cerebral autosomal-dominant arteriopathy, with subcortical infarcts and leukoencephalopathy (CADISIL) (188) and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke (MELAS) (189).

Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme in the metabolism of homocysteine, derived from the amino acid methionine. Homozygotes from the common MTHFR 677C>T variant have elevated homocysteine, where dietary intake of folic acid is moderate to low (190). Elevated homocysteine has been associated with disrupted endothelial function and risk of CVD (191-193). Elevated homocystein has been proposed as a link in migraine initiation (192, 194). Some studies have found an association between MTHFR 677C>T polymorphism (the TT genotype) and increased odds of having migraine and MA in particular (187, 195-199), but other studies have not found this association (200-202). The largest of these studies, a recent genetic association study among participants in the Women's Health Study (over 27 000 participants), was performed with information on 77 previously characterized polymorphisms implicated in CVD (203). The MTHFR 677C>T variant was not associated with migraine or aura status in this study. Although several polymorphisms were associated with migraine and migraine with aura, but after correction for multiple testing using the false discovery rate, none of the results remained significant. The results suggested a plausible association of polymorphisms implicated in inflammatory pathways (Tumour Necrosis Factor (TNF), Chemokine receptor 2 (CCR2), Transforming growth factor-beta 1 (TGFB1), Interleukin 9 (IL-9)) and migraine in women (203). The odds ratios in the above study were of small-effect size, which is in line with the notion that migraine is a complex heterogeneous disorder (203).

As mentioned earlier, cortical spreading depression, the presumed substrate of migraine aura, may predispose to brain lesions by reducing cerebral blood flow and by activating a cascade of inflammatory events (158). But it is not obvious how cortical spreading depression is involved in vascular events outside the brain, for example, ischaemic heart disease.

Migraine may directly cause an ischaemic event that is a migrainous infarct, but such events are rare, about 3% of all strokes (204), and can therefore only account for a small proportion of all strokes in migraineurs. Migrainous infarction has been estimated to have an incidence rate of 3 events per 100 000 per year (204) versus 2 events per 1000 per year for stroke (89).

The possibility that migraine and stroke share an underlying mechanism has been proposed (97, 187, 205-207). Both involve the release of vasoactive peptides (208) and enhanced platelet activity (209). During the aura phase of a migraine attack a constriction of blood vessels occurs, resulting in cerebral blood flow reduction (210), and when combined with vasoactive compounds like ergot alkaloids and triptans, the susceptibility for coagulopathies and risk of arterial thrombosis may increase (211). Increase in platelet aggregability and elevated von Willebrand factor have also been suggested to play a role in development of CVD (212, 213).

The migraine with aura subtypes, familial hemiplegic migraine and basilar migraine have been contraindications for ergotamin and triptan use (214) because of potential vasoconstriction leading to stroke, and triptan and ergotamin use, in general, is contraindicated in migraineurs with risk factors for CV disease (165, 215).

Some studies have shown migraineurs treated with triptans to be at increased risk of ischaemic stroke (216) and stroke of any cause (217, 218). Some studies and case reports have shown migraine to be associated with myocardial infarction (219-223) although a recent meta-analysis did not show a positive association (67). Other studies, where potential adverse CV disease effects of triptans did not show those treated at increased risk of any ischaemic events, including myocardial infarction and stroke or mortality (68, 71). But ergot alkaloids use was associated with non-significant increased risk of stroke compared to migraineurs that did not use ergot alkaloids (71).

In the current study men and women with MA are found at increased risk of CV disease mortality, but not men and women with MO. The question then arises whether migraine treatment could be the reason for this increased mortality among MA subjects. There is no data on migraine-specific medication in our study. We cannot therefore address this question. Another point coming to mind is whether the level of migraine treatment is different for MA and MO subjects. A search of the literature did not turn up such a comparison.

There is increasing evidence that migraine is associated with coronary heart disease (70, 91), and migraine has been reported to be associated with increased prevalence of vascular risk factors, such as smoking, unfavourable cholesterol profile and elevated blood pressure (78, 224). Current data show little difference in risk factors between those with and without migraine, which is in line with previous studies on migraineurs in the Reykjavik Study (99, 100). Our results were similar, with and without adjustment for conventional risk factors for cardiovascular disease – suggesting that the mechanism(s) linking migraine to CV disease are from a different pathway.

Others have reported that migraineurs, even or particularly (225) in the absence of conventional risk factors, have decreased cerebral and peripheral vascular resistance, retinal microvascular signs, hypercoagulability, and inflammation (97, 226, 227), supporting the hypothesis that migraine may be a systemic disorder that is affecting the vasculature. Migraineurs have been shown to have altered vascular reactivity present already at a young age (24.6 years) (228), which indicates that there may be a factor affecting both the onset of migraine and progression of cardiovascular disease early in life. These may also be coexisting phenomena. In a recent study migraineurs without aura were reported to have a reduced number of endothelial progenitor cells and reduced progenitor cell function migraineurs with aura (MA) had a further decrease, compared with MO subjects (226). A reduced number of endothelial progenitor cells in subjects with CHD has been associated with increased CV disease mortality and increased Framingham risk score (229). A reduced number of endothelial progenitor cells has also been reported to be associated with CV mortality.

Other proposed mechanisms include cardiac abnormalities, such as patent foramen ovale (PFO) (97, 230), a risk factor for stroke in young individuals (231), and has been reported to be more common in stroke patients with migraine younger than 55 years of age (161, 232). The only prospective sham-controlled study of PFO closure for MA was negative for all primary and secondary measures of migraine improvements (233). There are ongoing trials to determine if PFO closure has an effect on stroke recurrence, such as in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) Trial (234) and the PC-Trial (Patent foramen ovale and Cryptogenic embolism) (235). It must be noted that even if PFO closure turns out to be associated with stroke it will not explain the association between migraine and CHD.

The possibility of a false association due to a diagnostic artefact has also been raised (97, 157), but, given the increasing number of publications in the field of migraine and CVD, this possibility is unlikely.

In Figure 14 the conceptual mechanisms of migraine CVD association is shown as a spurious association (A), consisting of a unidirectional causal relationship either from migraine to CVD or from CVD to migraine (B), involving shared environmental risk factors causing both migraine and CVD (C), and involving shared genetic or biologic risk factors causing both migraine and CVD (D). From the mechanisms listed above the association between migraine and CVD is likely to be complex and may involve several mechanisms. Of the four options proposed in Figure 14, a combination of (C) and (D) is plausible, involving both genetic and environmental risk factors.

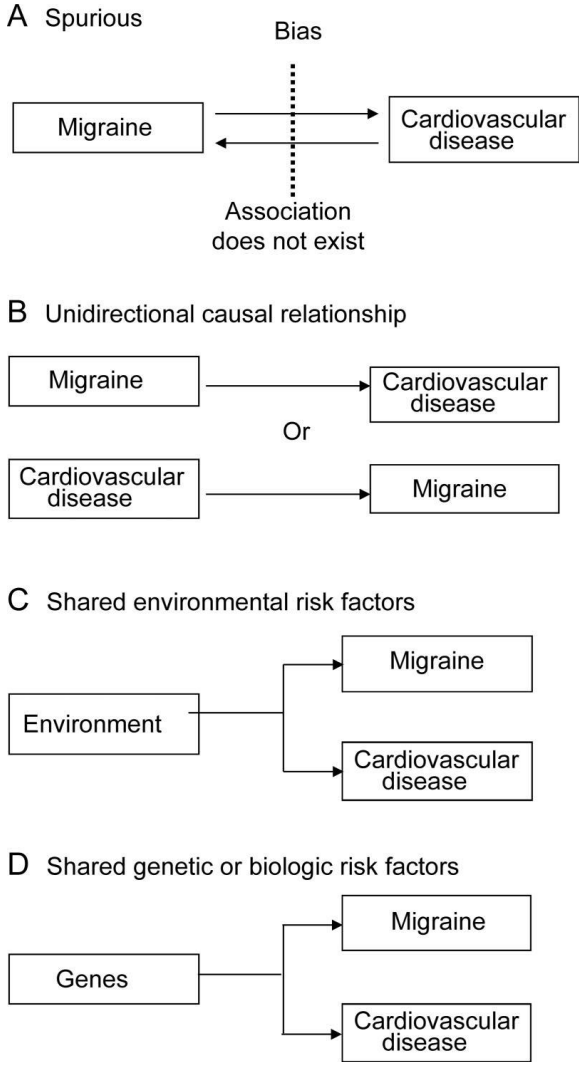

Figure 14: Conceptual mechanisms of the relationship between migraine with aura and cardiovascular disease. (From Bigal et al., Neurology 2009 (224)).

4.11 Strengths and weaknesses

Our study has significant strengths. Although the migraine classification in our study precedes the 2004 IHS criteria, the questions are similar to those currently asked in the IHS criteria and cover the most common migraine symptoms. The cohort is large, with a broad age range, and has comprehensive data on conventional CV risk factors at baseline as well as a very high ascertainment (>99%) of cause-specific mortality. The cohort is population-based, which adds to the generalisability of our results.

In regards to migraine at midlife in association with late-life brain infarcts, the participants were aged 33 to 65 when headache assessment was performed. At those ages, many participants were still experiencing migraines; recall bias is therefore likely reduced. Participants were also at low risk for TIA or stroke, making the identification of migraine visual aura symptoms more robust.

Potential limitations of our study of migraine and mortality should be taken into account. Questions on migraine symptoms were not asked of those reporting headache less than once per month; we are therefore likely to capture only those with a higher attack frequency. Those with migraine aura exclusively, without headache, would be included in the "no headache" group due to our screening question. Conclusions cannot be drawn from the current study about the mortality risk for migraineurs with low attack frequency (<1 attack per month) and those with migraine aura without headache.

The risk of cardiovascular outcomes may be higher in migraine sufferers with more frequent attacks. Kurth et al. looked at migraine attack frequency and CVD risk in a cohort of US women (236). They reported a J-shaped association between migraine attack frequency and CVD risk. If this J-shaped association applies to the current study, our estimates may be somewhat lower than what we would have found if all migraine sufferers were included although this is speculative.

The prevalence of aura (as a proportion of the total migraine population) is higher than has been reported in other population studies and may include frequently occurring nonspecific visual symptoms such as blurring. The result of this misclassification is likely to attenuate the relationship between migraine with aura and mortality. We note that our prevalence of migraine overall (with and without aura combined) is highly consistent with prior studies (63).

The combination of visual symptoms and headache can be symptoms of a transient ischaemic attack (TIA). If TIA were misclassified as migraine with aura in our study, it might exaggerate the association between migraine and CVD mortality. However, our diagnosis of migraine required headache at least once a month during the last 12 months, which is not a feature of TIA. Therefore we believe it is unlikely that this type of misclassification would have appreciably affected the results reported herein.

As we only have data on baseline vascular risk factors, we did not adjust for potential changes in vascular risk factors that might have developed after initiating the study. We note that these risk factors in adults tend to track over time (237), that is, those at high risk tend to stay at high risk during follow-up, and those at low risk tend to stay at low risk. While residual confounding due to imperfect control for vascular risk factors at baseline or after study initiation is a possibility, we note that the hazard ratios scarcely changed after adjustment – arguing against a strong role for this sort of error.

Although only about 2% of migraineurs have new-onset migraine over the age of 50 (146), the younger persons in the cohort may have developed migraine after the study started and not been counted as migraineurs. We suggest that such a low percentage of migraineurs would be unlikely to change the risk estimates in the current study. Neither data on migraine-specific treatment, such as ergotamine and triptans, nor data on the use of analgesics or medical steroids were available; the potential modifying effects of these medications on the association between migraine and CV disease could therefore not be estimated in the current study.

5 CONCLUSIONS

5.1 Conclusions

Migraine and hypertension, migraine and blood pressure

In a population-based study of men and women, no clear association was found between migraine and hypertension. It was found that subjects with migraine had lower pulse pressure, lower SBP and higher DBP, compared with controls. The association between blood pressure and migraine was stronger among women than men.

Migraine and CRP

CRP levels were not increased among migraine sufferers, compared with nonmigraineurs. Migraineurs without aura tended to have lower CRP values than nonmigraineurs and migraineurs with aura, except for young women migraineurs without aura, who had borderline higher CRP levels, compared with migraineurs with aura and nonmigraineurs. The association between CRP and migraine status was similar among those developing coronary heart disease during follow-up and those who did not.

Migraine and brain infarcts

This study suggests that a remote history of migraine with aura is associated with brain lesions commonly found in older populations. Results persisted after controlling for cardiovascular risk factors and history of cardiovascular disease, thus suggesting that the mechanism linking the migraine aura with these lesions is independent of the usual risk factors for ischaemic vascular disease and may be specifically related to migraine with aura.

Migraine and CV- , non-CV- and all-cause mortality

In this cohort study with over 470 thousand person-years and a median follow-up of 26 years, men and women with migraine with aura were shown to be at increased risk of all-cause and CV mortality, while migraineurs without aura were not at increased risk. Risk of CV mortality was marginally more elevated in men than women with migraine and aura. When CV mortality was examined further, subjects with MA were at increased risk of both CHD and stroke mortality. The increased risk of CV mortality observed among migraineurs vs. those with no headache in current study was neither explained by differences in BP levels nor differences in CRP levels.

Women with MA were at increased risk of non-CV mortality, which was not due to increased risk of cancer but increased risk of non-CV mortality other than cancer. This is a novel finding requiring confirmation in another cohort.

Data from the Reykjavik Study on CV mortality were used to update a meta-analysis. There was significant heterogeneity in the results for case-control and cohort studies combined, and cohort studies were therefore analyzed separately. Updated meta-analysis using cohort studies showed both men and women at increased risk of CV mortality.

Migraine with aura is an independent risk factor for cardiovascular and all-cause mortality in both men and women but was weaker than major established risk factors, such as cigarette smoking, diabetes and high blood pressure.

5.2 Implications for clinical practice

Migraineurs, and migraineurs with aura in particular, are at a modestly increased risk of mortality, independent of classical cardiovascular disease risk factors measured in mid-life. Even so it should be stressed that the absolute risk is low, and the focus should be on conventional risk factors, such as hypertension, smoking and adverse lipid profile, when reducing CV risk, regardless of migraine status.

5.3 Future directions

Further studies are needed to explore why increased prevalence of hypertension is found in some cohorts but not in others. The association between migraine and pulse pressure needs to be studied further in order to establish the mechanisms involved. Migraineurs have been shown to have altered vascular reactivity even at an early age (228), which indicates that there may be a factor affecting both the onset of migraine and progression of cardiovascular disease early in life; more studies are needed in this area.

Current study did not find an association between migraine and CRP. Still, there are studies showing inflammation responses during migraine attack that need further exploration. For example, interleukin 6 (IL-6) and IL-10 have been shown to increase during migraine attacks (238). IL-6 and IL-10 are cytokines, which have been found to have a pain-mediating function as well as an immunological function. Other biomarkers that should be studied further include von Willenbrand factor and endothelial glycoprotein that is important in the balance between coagulation and

fibrinolysis (239), which has been documented to rise during migraine (240) as well as between migraine attacks (213).

Additional longitudinal studies with repeated MRIs are needed to better establish the temporality and dose response relationship between migraine with aura and brain infarcts. Studies in elderly subjects without migraine have shown silent brain infarcts and white matter lesions to be associated with dementia and cognitive decline (241, 242). The clinical implications of the infarct-like lesions identified among migraineurs have not been established and will require investigation.

More research is needed on the association between migraine and CV-, non-CV and all-cause mortality, including studies to identify whether there are specific sub-groups of migraineurs who are at particular risk due to genetic or environmental factors. Future studies should have a more detailed assessment of aura status and attack frequency, and prospective studies can monitor CV risk profile changes over time in order to better understand the aetiology and pathophysiology of migraine in the development of CVD. Finally, future studies are needed to determine if reducing attack frequency by preventive treatment for migraine might reduce the risk of cardiovascular disease in migraineurs.

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PAPERS I-IV

Paper I

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Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21 537 subjects. The Reykjavik Study

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Cephalalgia

Gudmundsson LS, Thorgeirsson G, Sigfusson N, Sigvaldason H & Johannsson M. Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21 537 subjects. The Reykjavik Study. Cephalalgia 2006; 26:436–444. London. ISSN 0333-1024

Several studies have explored a possible association between migraine and hypertension, with contradictory results. Because of this uncertainty the relation between blood pressure (BP) and migraine was studied in 10 366 men and 11 171 women in a population-based longitudinal study. A modified version of the 1988 International Headache Society criteria was used for diagnosis of migraine. Logistic regression analysis was used. The crude 1-year prevalence of migraine was 5.2% among men and 14.1% among women. No significant association was found between hypertension and migraine. For a one standard deviation (SD) increase in diastolic BP the probability of having migraine increased 14% ($P = 0.11$) for men and 30% ($P < 0.0001$) for women. For a 1-SD increase in systolic BP the probability of having migraine decreased 19% ($P = 0.007$) for men and 25% ($P < 0.0001$) for women. It was also found that for a 1-SD increase in pulse pressure the probability of having migraine decreased 13% ($P = 0.005$) for men and 14% ($P < 0.0001$) for women. In a population-based study of men and women it was found that subjects with migraine had lower pulse pressure, lower systolic BP and higher diastolic BP compared with controls. □*Antihypertensive treatment, blood pressure, cohort, hypertension, men, migraine, women*

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Introduction

Several studies have explored a possible association between migraine and hypertension, with contradictory results. Some studies have shown a positive association between migraine and hypertension (1–5), others have shown no difference in prevalence of migraine between hypertensive and non-hypertensive subjects (6–8). Two recent studies found a significant negative association between migraine and hypertension (9, 10).

When looking at association between migraine and blood pressure the results have also been contradictory. Case–control studies have shown a positive association between migraine and systolic blood pressure (SBP) (11) and both SBP and diastolic blood pressure (DBP) (12).

In a cross-sectional epidemiological study the relation between DBP and SBP, respectively, and migraine was examined. No significant difference in SBP was found, but women migraineurs had higher DBP than non-migraineurs. This difference was not found for men (8). It has also been found that migraine was more frequent in individuals with normal blood pressure compared with high blood pressure (9). A recent population-based longitudinal study showed that participants with migraine had lower SBP and lower mean arterial pressure, and

significant trend of decreasing frequency of migraine with increasing SBP (10). Other epidemiological studies have not shown a clear association between blood pressure and migraine (6, 13).

Possible reasons for some of these contradictory results may be differences in definition of migraine and hypertension, differences in blood pressure measurement procedures and differences in sample size. The methods for comparison in these studies vary also, some comparing migraine with SBP or DPB alone and others with SBP and DBP combined.

Because of the uncertainty of the association between migraine and hypertension, and migraine and blood pressure this possible association was studied, using data from The Reykjavik Study. The study provides an opportunity to re-examine the association between migraine and hypertension and migraine and blood pressure in a large population-based study, thus allowing stratification by sex, focusing on systolic, diastolic, mean arterial and pulse pressure.

Methods

The study was performed in accordance with the Helsinki Declaration and was approved by the National Bioethics Committee and the Data Protection Authority in Iceland. All participants gave informed consent.

People invited to participate in the Reykjavik Study were all the legal residents in the Reykjavik area on 1 December 1966. The men were born in the following years: 1907, 1910, 1912, 1914, 1916, 1917, 1918, 1919, 1920, 1921, 1922, 1924, 1926, 1928, 1931 and 1934; the women 1 year later, i.e. 1908, 1911, etc. Both sexes were divided into groups A, B and C according to birthday, i.e. those in group B were born on the 1st, 4th, 7th, etc., of each month, those in group C were born on the 2nd, 5th, 8th, etc., of each month, and those in group A were born on the 3rd, 6th, 9th, etc., of each month (see Fig. 1). Groups D, E and F comprised people born in the years previously omitted in the period 1907–1935, excluding those years listed above and divided in the same manner as A, B and C. The study population thus comprised all men born in the years 1907–1934 and all women born in the years 1908–1935 living in the Reykjavik area on 1 December 1966. The study was performed in six stages. The first took place in 1967–1969, the second in 1970–1972, the third in 1974–1979, the fourth in 1979–1984, the fifth in 1985–1991 and the sixth in 1991–1996. Group B was invited to participate in the first five stages of the study, group C in stages 2 and 3, group A in stage 3, group D in stage 4, group E in stage 5, and those in group B and who had reached the age 70 in 1991 (men) or 1993 (women) participated in stage 6. One of the original aims of the Reykjavik Study was to assess the health benefits to be gained from such mass screening programmes. Therefore one group (B) was invited to be examined repeatedly. Figure 1 shows the years for examination for each group. The number of subjects alive at midpoint of each stage was used to calculate response rate. In the six stages 9328 men were invited 26 071 times to be examined, which resulted in 18 494 examinations, an average response rate of 70.9% (range 64.6–75.25%). Ten thousand and sixty-two women were invited 26 080 times, which

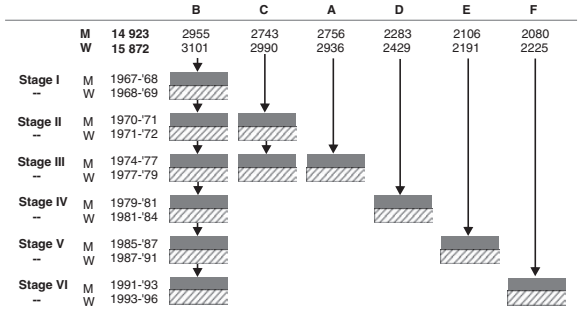

Figure 1 Study plan of the Reykjavik Study. The selected population were all men (M, $n = 14\,923$) with legal residence in Reykjavik and the surrounding area on 1 December 1966, who were born 1907–1934. The women (W, $n = 15\,872$), selected from the same area, were born 1908–1935. The men and women were divided into groups labelled A–F. The numbers shown represent the number in each group. The hatched and shaded boxes show when subjects in each group were examined.

resulted in 18 281 examinations, an average response rate of 70.1% (range 66.8–76.9%) (14, 15). In this study only the first examination for each subject was used.

In order to look at subjects younger than in the Reykjavik Study, a new sample was selected in 1972, the Reykjavik Study for the young. It comprised equal groups of men and women, 2781 in all, born 1940–1954 (a stratified sample of subjects born in 1940, 1944, 1945, 1949, 1950, 1954). The subjects were invited to be examined in the years 1973–1974 and again in 1983–1985. Only the first examination was used. The number of subjects that were examined at least once was 1038 men and 1109 women. Combining the subjects from the Reykjavik Study and the study for the young, the total number of men was 10 366 and of women 11 171, and their ages were 19–87 years.

Every participant received an invitation letter that included standardized questions about health and social factors.

Examinations

Participants came in a fasting state to the clinic. After a 5-min rest, the supine blood pressure was measured, on two occasions, between 08.30 and 10.30 h, by a nurse, and 10–14 days later between 11.00 and 13.30 h, by a physician. Subjects were not instructed to be fasting at the second blood pressure measurement. The instruments used were mercury sphyngomanometers of the type 'Erkameter' wall-model (Erka, Germany). The cuffs had a rubber bladder 15×32 cm, and the total length of the cuff was 66 cm. The same types of cuffs and instruments were used throughout the study. The procedure followed in measuring blood pressure was according to World Health Organization recommendations (16). The diagnosis of hypertension was based on the mean of two measurements: SBP $\geq$ 160 mmHg and/or DBP $\geq$ 95 mmHg. Subjects on antihypertensive medication were considered hypertensive.

Definition of migraine

In this study a modified version of the 1988 International Headache Society (IHS) criteria was used (17). The questions on headache in the study questionnaire have been the same throughout the study. The questions are as follows.

Questions concerning symptoms during the last 12 months:

Do you get headache once or more per month? If YES, please answer the following questions.

1 Is the pain usually in one side of the head?
2 Do you feel nauseated or vomit when you get the headache?
3 Do you get visual disturbances simultaneously or shortly before the pain starts?
4 Do you get photophobia during the headache attack?
5 Do you get numbness in one side of the face or numbness in either arm before the headache begins?

Subjects were considered to have migraine 'loose criteria' if answering yes to any two or more of questions 1–5.

A 'stricter criterion' was also made where a subject had to answer yes to any three or more of questions 1–5.

The questionnaire of the present study was composed in 1967 and has to be compared with the more modern 1988 IHS criteria (17). The main differences are that in the present questionnaire questions are missing about duration, intensity, phonophobia and pulsating quality of the headache. Also missing are questions about the less common symptoms of unilateral weakness and speech difficulty.

Statistics

Information on subjects at first visit was used in a logistic regression model. All regression analyses were performed separately for men and women. When calculating odds ratios (ORs), adjustments were made for age and year entering the study. Age was entered into the model as a continuous variable and as a categorical variable (12 categories and six categories). Comparing the Deviance (– 2 log likelihood) of the two models, using a χ^2 test, age in 12 categories of 5 years each gave the best fit. DBP and SBP were introduced separately and jointly to the model. The model containing both SBP and DBP gave the best fit and was therefore used to estimate the effect of SBP and DBP on odds of having migraine. Pulse pressure (PP) was defined as SBP – DBP and mean arterial pressure as (1/3 SBP + 2/3 DBP).

To see if educational level was a confounder, four educational levels were identified in the questionnaire: elementary school or less, high school education, junior college education and university education, and used in the logistic regression model. Also to see if smoking was a confounder, smoking was entered into the logistic regression model as: never smoked, former and current smoker.

Collinearity (to see if there was a relationship among the predictor variables that did not involve

the response variable) between SBP and DBP was analysed by calculating condition numbers from variance–covariance matrix of the predictor variables and the variance component of each predictor variable. Significance testing was two-sided and based on a 5% probability level. Thus, results are presented with 95% confidence intervals (CI). The software package used was SPIDA (18).

Results

Prevalence of migraine

The crude 1-year prevalence of migraine among men using loose and strict criteria of migraine was 5.2% and 2.1% and for women the prevalence was 14.1% and 8.0%, respectively. The corresponding 1-year prevalence of migraine for men, adjusted to Segi World population (19, 20) using loose and strict criteria, was 5.7% and 2.3% and for women the prevalence was 16.4% and 8.0%, respectively. The age- and sex-specific 1-year prevalence of migraine using loose and strict criteria of migraine in the Reykjavik study can be seen in Fig. 2. The subject's characteristics at first visit can be seen in Table 1. There are some differences in BP levels between groups but these differences are not adjusted for age, examination year and antihypertensive medication use.

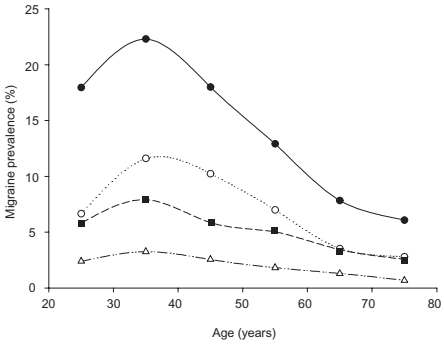

Figure 2 Age- and sex-specific 1-year prevalence of migraine in the Reykjavik Study, 1967–1996. Prevalence of migraine, defined by a modified version of the 1988 International Headache Society criteria, in a cohort of 10 366 men and 11 171 women. Loose criteria of migraine: answering yes to two or more out of five questions on migraine, men (■, $n = 543$) and women (●, $n = 1573$). Strict criteria of migraine: answering yes to three or more out of five questions on migraine, men (Δ, $n = 214$) and women (○, $n = 826$).

Migraine and hypertension

Using loose criteria, hypertension was not associated with migraine, OR 0.97 (95% CI 0.79, 1.19) for men and 1.03 (95% CI 0.89, 1.18) for women. When excluding those on antihypertensive medication, the ORs were lower but not significantly lower than one, OR 0.83 (95% CI 0.66, 1.06) and 0.93 (95% CI 0.78, 1.12), respectively.

When dichotomizing on SBP ≥ 160 mmHg, using loose criteria of migraine (adjusting for age and antihypertensive medication use), there was no association with migraine for men, OR 0.93 (95% CI 0.71, 1.22). However, for women there was a significant inverse association, OR 0.76 (95% CI 0.62, 0.92).

When dichotomizing on DBP ≥ 95 mmHg (adjusting for age and antihypertensive medication use), there was no association with migraine for men or for women, OR 0.89 (95% CI 0.71, 1.12) for men and 1.02 (95% CI 0.86, 1.21) for women.

Migraine and blood pressure

In Fig. 3 the association between blood pressure and migraine, using loose and strict criteria of migraine, can be seen. Due to lower sample size in the groups defined by the stricter criteria, the CIs for the odds ratios were wider than for the odds ratios in the groups defined by the loose criteria. SBP was significantly negatively associated with migraine but DBP was not. There was no significant association between migraine and mean arterial pressure. However, there was a significant negative association between pulse pressure and migraine for both men and women. When looking at the association between SBP and migraine for men and women, adjusting for DBP (see Fig. 3), an increase in SBP was associated with decreased prevalence of migraine. On the other hand, when looking at an association between DBP and migraine for men and women, adjusting for SBP (see Fig. 3), an increase in DBP was associated with increased migraine prevalence. When SBP and DBP were both in the logistic regression model there was a consistency between using loose and strict criteria of migraine both for men and women. There was a stronger association between blood pressure and migraine amongst subjects defined by strict criteria of migraine than amongst those defined by loose criteria (Fig. 3). Comparing the deviance of the regression models for men and women between blood pressure and migraine, the models giving the best fit were those containing both SBP and DBP and the model containing pulse pressure only, but the

Table 1 Characteristics at first examination of men ($n = 10\,366$) and women ($n = 11\,171$) in the Reykjavik Study 1967–1996

	Men			Women		
Characteristics	No migraine Mean ± SD	Loose criteria Mean ± SD	Strict criteria Mean ± SD	No migraine Mean ± SD	Loose criteria Mean ± SD	Strict criteria Mean ± SD
Age	50.6 ± 11.6	47.8 ± 11.0	46.9 ± 11.3	52.2 ± 12.4	47.9 ± 11.4	48.2 ± 10.7
Systolic blood pressure	139.8 ± 18.8	137.0 ± 18.0	136.9 ± 17.3	136.7 ± 20.8	132.8 ± 18.9	132.6 ± 18.1
Diastolic blood pressure	87.3 ± 10.5	86.9 ± 10.6	87.7 ± 10.5	83.1 ± 10.3	82.8 ± 10.6	83.1 ± 10.1
Mean arterial pressure	104.8 ± 12.4	103.6 ± 12.3	104.1 ± 12.2	100.9 ± 12.9	99.4 ± 12.4	99.6 ± 11.9
Pulse pressure	52.5 ± 13.0	50.0 ± 11.7	49.3 ± 10.6	53.6 ± 14.7	50.1 ± 12.8	49.5 ± 12.4
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total number of subjects	9823 (100)	543 (100)	214 (100)	9598 (100)	1573 (100)	826 (100)
Headache	1728 (17.6)	543 (100)	214 (100)	2707 (28.2)	1573 (100)	826 (100)
Pain, unilateral	484 (4.9)	390 (71.8)	175 (81.8)	694 (7.2)	1134 (72.1)	675 (81.7)
Nausea/vomiting	64 (0.7)	241 (44.4)	146 (68.2)	211 (2.2)	1048 (66.6)	667 (80.8)
Visual disturbances	106 (1.1)	314 (57.8)	175 (81.8)	120 (1.3)	812 (51.6)	598 (72.4)
Photophobia	120 (1.2)	327 (60.2)	175 (81.8)	196 (2.0)	1055 (67.1)	698 (84.5)
Numbness	19 (0.2)	116 (21.4)	59 (27.6)	29 (0.3)	367 (23.3)	283 (34.3)
Elementary school or less education	3274 (33.3)	189 (34.8)	67 (31.3)	4895 (51.0)	781 (49.7)	491 (50.7)
High school education	4382 (44.6)	247 (45.5)	106 (49.5)	3789 (39.5)	641 (40.8)	334 (40.4)
Junior college education	1229 (12.5)	70 (12.9)	26 (12.2)	751 (7.8)	125 (8.0)	59 (7.1)
University education	938 (9.5)	37 (6.8)	15 (7.0)	166 (1.7)	26 (1.7)	14 (1.7)
Current smoker	2362 (24.0)	136 (25.0)	56 (26.2)	1505 (15.7)	260 (16.5)	136 (16.5)
Former smoker	5295 (53.9)	295 (54.3)	113 (52.8)	3847 (40.1)	641 (40.8)	321 (38.9)
Hypertension	2728 (27.8)	135 (24.9)	55 (25.7)	2352 (24.5)	313 (19.9)	160 (19.3)
On antihypertensive medication	658 (6.7)	43 (7.9)	21 (9.8)	1063 (11.1)	140 (8.9)	74 (9.0)

Hypertension: blood pressure ≥ 160 and/or 95 mmHg or on antihypertensive medication.

Subjects with the definition 'loose criteria' for migraine ($n = 543$ for men and $n = 1573$ for women) include subjects with the definition 'strict criteria' for migraine.

model with mean arterial pressure gave the highest deviance (data not shown).

Possible confounders

The introduction of educational level into the model did not change the association between pulse pressure and migraine significantly and was therefore left out of the model (P for difference in β coefficients, $P = 0.99$ for men and $P = 0.93$ for women, t-test).

Relative to those who had never smoked, current smoking was not a significantly predictive variable in the model for migraine in relation to age, pulse pressure and antihypertensive medication for men ($P = 0.91$; OR 1.01, 95% CI 0.81, 1.27) or for women ($P = 0.96$; OR 0.96, 95% CI 0.85, 1.08). In the same model, former smoking was not significantly predictive of migraine for men ($P = 0.20$; OR 1.18, 95% CI 0.91, 1.54) or for women ($P = 0.13$; OR 1.13, 95% CI 0.97, 1.32). Smoking was therefore left out of the model.

The variables that were used for each sex in the final regression model were age and year of examination. Mean arterial blood pressure, pulse pressure, SBP and/or DBP were all analysed in relation to migraine adjusting for these variables.

A possible collinearity between SBP and DBP was considered. When checking for collinearity in a logistic regression model it is advisable to check condition numbers that are over 20 and to check the variance component for these values. It should be analysed further when the variance component exceeds 0.5 for more than one variable where the condition numbers are over 20. The condition numbers where SBP and DBP had variance component 0.8–0.9 was about 40. When SBP and DBP were normalized (i.e. the average was deducted and then divided by the SD), the regression was almost identical and the deviance also. Where SBP and DBP was dominant the condition numbers were only about 4 so there was not much concern for collinearity. Also, the correlation coefficient for SBP and DBP was 0.75 but is usually close to 0.99 when there is considerable collinearity.

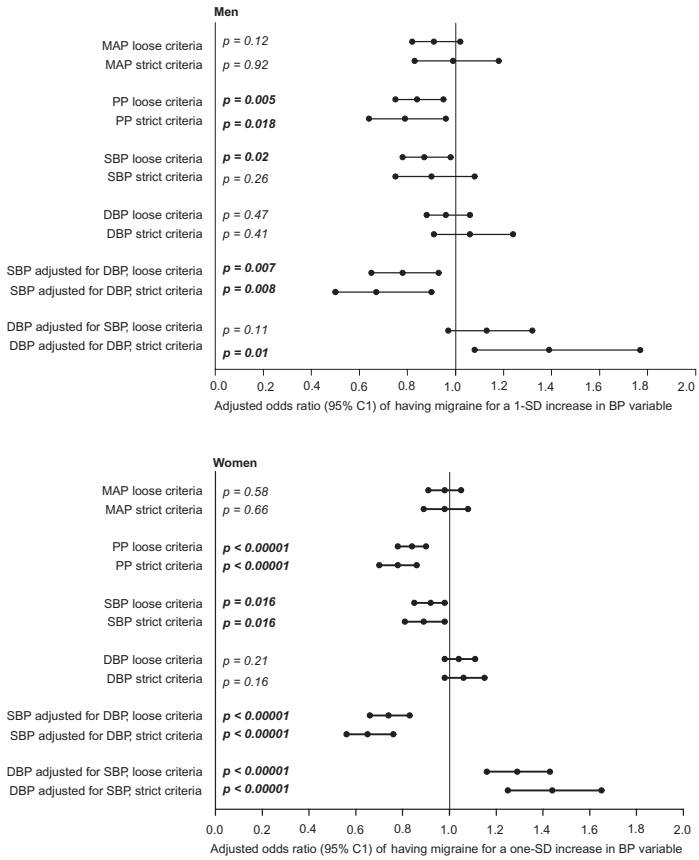

Figure 3 Adjusted odds ratio (95% confidence interval) of having migraine for a 1-SD increase in blood pressure variable. Systolic (SBP) and diastolic (DBP) blood pressure are entered individually and jointly into the regression model. Loose criteria of migraine: answering yes to two or more out of five questions on migraine, men ($n = 500$) and women ($n = 1433$). Strict criteria of migraine: answering yes to three or more out of five questions on migraine, men ($n = 193$) and women ($n = 752$). Adjustment is made for age and year of examination. Subjects on antihypertensive medication are excluded. PP, Pulse pressure; MAP, mean arterial pressure.

Discussion

In a population-based study of men and women there was no clear association between hypertension and migraine. Using logistic regression analysis, it was found that subjects with migraine had lower pulse pressure, lower SBP and higher DBP compared with controls.

Hypertension and migraine

This study showed no clear association between hypertension and migraine. Similar findings have been reported by others (6–8, 21). There was no association between migraine and diastolic hypertension but a negative association with systolic hypertension was found among women but not

among men. In 1988 the IHS published a new definition of migraine (17). Most studies on the association between hypertension and migraine were published before that date. Recently, two studies showed a negative association with migraine and hypertension. One found a negative association for both systolic and diastolic hypertension (9), but when adjusting for sex and confounding factors the association was marginally significant. The other found the negative association with migraine to be similar whether SBP ≥ 140/DBP ≥ 90 mmHg or SBP ≥ 160/DBP ≥ 95 mmHg was used as the definition of hypertension (10). Differences in these results may be due to different definitions of migraine (and hypertension) and to differences between populations and environmental factors.

Blood pressure and migraine

There was good consistency in the results between loose and strict criteria of migraine and blood pressure and between men and women (Fig. 3). When SBP or DBP was entered into the model, SBP was significantly negatively associated with migraine and DBP was not associated with migraine. This is in line with one recent study (10). But when entered jointly, DBP became positively associated with migraine and it gave significantly lower deviance, thus indicating it was a better model. When SBP and DBP were entered jointly into the regression model, the effect of increase in SBP could be seen when DBP was kept constant and *vice versa*. A positive association between DBP and migraine has been described before, but these studies did not report an inverse association between SBP and migraine (8, 13). An inverse association between SBP and migraine has recently been reported (9, 10), and in the first study there was also a inverse association between DBP and migraine (BP was defined as optimal normal, SBP < 130 and DBP < 85 mmHg, vs. high or above) (9), but in the second study the inverse association found between DBP and migraine was not significant (10). SBP being negatively associated and DBP being positively associated with migraine in the present study can possibly explain why many studies show no association between hypertension and migraine (6–8, 13). When an individual has systolic and diastolic hypertension the possible individual effect of SBP and DBP on migraine would cancel each other out. When comparing the deviance of different regression models it could be seen that SBP had a stronger association with migraine than DBP.

Pulse pressure was negatively associated with migraine both for men and women and to our knowledge this is the second study describing such an association. The first study (10) could not stratify by sex and did not adjust for antihypertensive medication use. It seems likely that the main connection between BP and migraine is through inverse association between SBP and migraine, because when adjusting for antihypertensive medication, systolic hypertension was negatively associated with migraine but diastolic hypertension was not. This, together with the results for the regression model that excludes subjects on antihypertensive medication, further supports that SBP has a stronger association with migraine than DBP.

Possible mechanism

The pathophysiological mechanisms behind migraine are poorly understood and while mechanistic explanations of the association between migraine and blood pressure are not available, some possibilities have emerged. There is some evidence for the involvement of calcitonin gene-related peptide (CGRP) in migraine (22). It has been found that the basal CGRP concentration in blood is higher in migraine patients (23), intravenous administration of CGRP can trigger a migraine attack (24) and a CGRP receptor antagonist is effective in the treatment of acute migraine attacks (22). As CGRP is a potent vasodilator (25), it seems possible that its involvement in migraine could explain some of the findings in the present study. Another possible mechanism is the involvement of serotonin (5-HT). Platelet serotonin has been found to be lower in migraineurs than in matched controls (26). Serotonin is mainly a vasoconstrictor which could also explain some of the findings of the present study. Other mechanisms could also be involved.

Strengths and limitations

The present study is large compared with many other studies on migraine. It also involves a relatively large proportion of an entire nation. The large number of subjects in the study and a relatively low number of subjects on antihypertensive treatment (<10%) allow omission of the antihypertensive-treated subjects when looking at the association between BP variables and migraine. The subjects are selected on basis of neither health nor socio-economic status and that gives the results more weight. Prevalence of migraine in this study is based on a modified version of the 1988 IHS

criteria. When comparing the modified version used and the IHS criteria there are several questions missing in the modified version for a definite diagnosis according to the 1988 IHS criteria. However, the questions used cover the most common migraine symptoms.

When using loose criteria of migraine the age-standardized 1-year prevalence for men and women of 5.7% and 16.4% is similar to what has been described for western countries, which is about 6% for men and 15–18% for women (27, 28). Preliminary results from a study of 2000 randomly selected Icelanders, using IHS criteria, showed a 7% and 19% prevalence of migraine for men and women, respectively (29). This prevalence is similar to the results in the present study. Age distribution for the 1-year prevalence of migraine is similar to what has been described by others (27, 30). The average 1-year prevalence and age distribution found in the present study gives some assurance that the sample is composed mainly of migraine patients.

This is a cross-sectional study and does not allow any inference of causality. Temporality is one of the factors missing for causality inference in a study of this kind and it is not possible to decide which comes first—the migraine or the changes in blood pressure.

Conclusions

In a population-based study of men and women, no clear association was found between migraine and hypertension. It was found that subjects with migraine had lower pulse pressure, lower SBP and higher DBP compared with controls. The association between blood pressure and migraine was stronger among women than men.

The mechanisms behind the association between migraine and blood pressure may involve CGRP, serotonin and other factors.

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Paper II

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C-reactive protein in migraine sufferers similar to that of non-migraineurs: the Reykjavik Study

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C-reactive protein (CRP), a marker of inflammation, has been associated with cardiovascular disease. Risk of cardiovascular disease is increased in migraineurs with aura. Results from a clinical report, case–control and a cohort study suggest that CRP is elevated in migraineurs compared with non-migraineurs. We examined the proposed association in a case–control study nested within two large population-based studies. The relationship between migraine and CRP (high-sensitivity CRP) was studied in 5906 men and women aged 55.0 ± 8.5 years in the Reykjavik Study and 1345 men and women aged 27.7 ± 5.5 years from the Reykjavik Study for the Young. A modified version of the International Headache Society's criteria was used to categorize people into migraineurs (two or more symptoms) or non-migraineurs. Migraineurs with visual or sensory symptoms were further defined as having migraine with aura (MA) or without aura (MO). Multivariable-adjusted CRP levels were similar in migraineurs and non-migraineurs for men (0.83 vs. 0.79 mg/l, $P = 0.44$) and for women (0.87 vs. 0.87 mg/l, $P = 0.90$). When further stratified by migraine aura and age, no differences were found between non-migraineurs, MO and MA among men. In women, CRP levels were borderline higher in those with MO compared with non-migraineurs and those with MA (1.01 mg/l vs. 0.81 and 0.75 mg/l, $P = 0.08$ and $P = 0.08$) in age group 19–34 years, but significantly lower in age group 60–81 years (0.52 mg/l vs. 1.07 and 1.01 mg/l, $P = 0.007$ and $P = 0.03$). CRP levels were not increased among migraine sufferers compared with non-migraineurs. Older women migraineurs without aura had lower CRP values than non-migraineurs and migraineurs with aura. □ *C-reactive protein (hs-CRP), cardiovascular disease, epidemiology, inflammation, migraine*

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Introduction

C-reactive protein (CRP), a marker of inflammation, has been associated with risk of cardiovascular disease (1). CRP has been suggested to be abnormal among migraineurs, possibly through repeated vascular inflammation (2). The risk of stroke and coronary heart disease is greater in migraineurs than in others, especially for those with aura (3, 4). There are limited data on the relationship between CRP and migraine.

Welch et al. performed a retrospective review of 60 migraineurs (90% female) with complex clinical features, who were referred to secondary or tertiary

clinics (2). The results indicated that 43% of the patients had elevated CRP (defined as > 3 mg/l), with a suggestion of a higher proportion in patients without aura (16/29, 55%) compared with patients with aura (10/31, 32%).

A case–control study of 50 young adult patients with migraine and 50 controls (78% female) showed that the median CRP level was 1.42 mg/l in migraineurs and 0.90 mg/l in controls ($P = 0.03$) (5). CRP was higher in the patients without aura than in controls: 2.11 mg/l vs. 0.90 mg/l ($P = 0.0002$).

Compared with women with no migraine history, women with a self-reported history of migraine had a modestly increased multivariable-adjusted odds ratio for elevated CRP in a large cohort study of female health professionals, aged ≥ 45 years [1.13, 95% confidence interval (CI) 1.05, 1.22] (6). Among current migraineurs, age-adjusted CRP was higher in the women without aura, compared with women with aura (4.08 vs. 3.86 mg/l).

Thus, the results from these three studies, a clinical report, a case–control study and one large cohort study of female health professionals, suggest that CRP is modestly elevated in migraineurs compared with controls. The results further suggest that the elevation is more evident for migraineurs without aura than those with aura.

In this study we further examined this potential relationship between CRP and migraine, with and without aura, in a case–control study nested within two large population-based cohorts of women and men ranging in age from 19 to 81 years.

Methods

Reykjavik Study briefly

The Reykjavik Study is a large, population-based cohort study, which started in 1967 (7). Men born 1907–1934 and women born 1908–1935, residing in the Reykjavik area and a few adjacent communities on 1 December 1966, were randomly selected for participation. A total of 19 390 persons agreed to take part, which was approximately 70% of all those invited. The study cohort, which was divided into six groups of men and women, was investigated at the Heart Preventive Clinic in Reykjavik during the period 1967–1996 [CRP was not measured in the sixth group ($n = 478$) and this group was therefore omitted from the analysis]. The first examination of each person occurred between 1967 and 1993 for men and between 1968 and 1996 for women. The age range at the time of CRP measurement was 33–81 years. The average year of examination used was 1974 S.D. 5.7 years (1967–1991).

In order to study subjects younger than the participants of the Reykjavik Study, a new sample was selected in 1972, the Reykjavik Study for the Young (8). This group comprised equal groups of men and women, 2781 in all, born 1940–1954. The subjects were invited to be examined three times in the years 1973–1974, 1983–1985 and 2001–2003. Those who participated in the third stage and had participated in either of the first two stages were sampled, and the first visit was used. The age range of the Reykjavik Study for the Young at the time of CRP measurement was 19–45 years. The present analysis is based on the CRP measured at the first examination. The number of subjects examined at least once was 1037 men and 1109 women. The average year of examination used was 1975 S.D. 3.8 years.

Combining the subjects from the Reykjavik Study and the Study for the Young, the total number of men was 10 171 and of women 10 878, and their ages at the time of measurement were 19–81 years.

Every participant received an invitation letter with standardized questions about health and social factors, including questions related to the presence of headache and headache features (see below).

The present analysis of the Reykjavik Study is based on a subset of participants who were selected for a nested case–control study of CRP and myocardial infarction (MI) (9). The cases were 2400 subjects without a history of MI at entry into the study who had a major coronary event during the mean (±S.D.) follow-up of 17.5 ± 8.7 years, compared with 20.6 ± 8.2 years among controls for the Reykjavik cohort. The controls were frequency-matched to the cases with respect to the year of recruitment, sex and age in 5-year increments (9). In all, 5906 subjects from the Reykjavik Study were used in the current analysis. For the Reykjavik Study for the Young, all cases ($n = 18$) and controls ($n = 1327$) with available CRP measurements were used. They had a mean follow-up of 20.9 ± 6.6 years for the cases and 28.2 ± 3.8 years for the controls.

Every participant received an invitation letter with standardized questions about health and social factors, including questions related to the presence of headache and headache features (see below).

Examinations

Participants came in a fasting state to the clinic. After a 5-min rest, supine blood pressure was measured twice, between 08.30 and 10.30 h, by a nurse,

and 10–14 days later between 11.00 and 13.30 h, by a physician. Subjects were not instructed to be fasting at the second blood pressure measurement. The instruments used were mercury sphygmomanometers of the type 'Erkameter' wall-model (Erka, Bad Tölz, Germany). The cuffs had a rubber bladder 15–32 cm, and the total length of the cuff was 66 cm. The same types of cuff and instrument were used throughout the study. Blood pressure was measured according to World Health Organization recommendations (10). Major coronary heart disease was defined as: death from coronary heart disease and non-fatal MI. Deaths from coronary heart disease were ascertained from central registers on the basis of a death certificate listing an International Classification of Diseases code of 410 to 414, and the diagnosis of non-fatal MI was based on the criteria of the Monitoring Trends and Determinants in Cardiovascular Disease study.

CRP measurements

Blood was drawn at the first visit, when subjects came in fasting. The concentration of CRP (high-sensitivity CRP, referred to as CRP in this study) was measured as described (9) by latex-enhanced immunoturbidimetry, with a lower limit of detection of 0.02 mg/l (Roche Diagnostics, Basel, Switzerland). The variation in CRP values within runs was < 1%, and the between-day variability was 1% at a concentration of 14 mg/l and 3.7% at a concentration of 3.8 mg/l (9). CRP measurements of samples in the Reykjavik Study and the Reykjavik Study for the Young were identical except for the recording of the CRP values; the former was recorded to two decimal points and the latter to one decimal point. We excluded subjects with CRP > 10 mg/l ($n = 313$) because values above this cut-point are usually associated with acute-phase stimulus (11), such as bacterial infection (12).

Definition of migraine

In this study a modified version (8) of the 1988 International Headache Society (IHS) criteria was used (13).

The questions on headache in the study questionnaire were the same for the original and younger Reykjavik cohorts. The questions were as follows.

Questions concerning symptoms during the last 12 months:

Do you get headache once or more per month?
If YES, please answer the following questions.

1. Is the pain usually on one side of the head?
2. Do you feel nauseated or vomit when you get the headache?
3. Do you get visual disturbances simultaneously or shortly before the pain starts?
4. Do you get photophobia during the headache attack?
5. Do you get numbness on one side of the face or numbness in either arm before the headache begins?

Subjects were considered to have migraine by 'relaxed criteria' if they answered yes to any two or more of questions 1–5 (8). Subjects were considered to have migraine by 'strict criteria' if they answered yes to any three or more of questions 1–5 (8). Migraineurs 'relaxed criteria' with visual or sensory symptoms (questions 3 and 5) accompanied by other symptoms were further defined as having migraine with aura (MA), those without visual or sensory symptoms were defined as migraineurs without aura (MO).

The questionnaire of the present study was composed in 1967. No questions were asked about the duration, intensity, phonophobia or pulsating quality of the headache, which are part of the IHS criteria from 1988 (13). Also missing were questions about the less common symptoms of unilateral weakness and speech difficulty.

Analysis

We compared the average CRP between subjects with migraine (with or without aura) and those without migraine, using linear regression. As the distribution of CRP was log-normal, we transformed CRP in all linear regression models.

All regression analyses were performed separately for men and women and performed separately within each age category (four age categories, 19–34, 35–49, 50–59 and 60–81 years). Adjustments were made for case–control status, age, body mass index (calculated as weight in kg divided by height in m^2), cholesterol, smoking status (never smoked, former smoker, current smoker), education (elementary school or less, high school education, junior college or university education), current hormone use, current diabetes mellitus, systolic blood pressure (SBP) and antihypertensive therapy. SBP and antihypertensive use were in three categories: (i) SBP < 130 mmHg; (ii) SBP 130–160 mmHg; and (iii) SBP ≥ 160 mmHg and/or antihypertensive use. For women adjustment was made for oral contraceptive use, which has been shown to be associated with

CRP levels (14). Adjustment for physical exercise (defined as 0, 0–5 and ≥ 6 h per week) was made but the variables listed above were stronger predictors of CRP levels in the regression model, and physical exercise was therefore left out of the final model. In addition, we tested for cohort difference in the association of CRP with migraine. The age group represented both in the Reykjavik Study and in the Reykjavik Study for the Young was used to estimate a possible cohort effect. A linear regression model with log-transformed CRP as a function of migraine status was used. In a multivariable-adjusted model for men, aged 30–39 years ($n = 139$) in the Reykjavik Study and ($n = 186$) in the Reykjavik Study for the Young, cohort was not a significant variable ($P = 0.30$). Similarly for women, ($n = 84$) for the Reykjavik Study and ($n = 62$) for the Reykjavik Study for the Young, cohort was not a significant variable ($P = 0.76$) in the model.

The above analysis was also performed for subjects who were not diagnosed with a major coronary event during follow-up.

Significance testing was two-sided and based on a 5% probability level. Thus, results are presented with 95% CI. The software package used was STATA version 9 (StataCorp LP, College Station, TX, USA).

Results

Migraine prevalence

Table 1 shows characteristics of the study population, consisting of the subset of the Reykjavik Study and the Reykjavik Study for the Young participants with available CRP measurements. The crude 1-year prevalence of migraine (relaxed criteria) was 5.0% among men and 14.3% among women. This prevalence was similar to that of migraine in the whole cohort (5.2% men, 14.1% women, Fig. 1) (8). The prevalence of MA was 3.6% for men and 8.8% for women (see Table 1).

CRP values

After excluding subjects with CRP > 10 mg/l ($n = 313$), the median CRP value for all other subjects in the Reykjavik Study ($n = 5906$) was 1.31 mg/l (25th and 75th percentile 0.63 and 2.68 mg/l), and the corresponding median CRP value for subjects ($n = 1345$) in the Reykjavik Study for the Young was 0.6 mg/l (25th and 75th percentile 0.3 and 1.4 mg/l).

Age- and multivariable-adjusted CRP values for non-migraineurs, migraineurs, MO and MA subjects are shown in Table 2. Age-adjusted values among men were borderline lower for MO subjects compared with non-migraineurs, and the values for MA subjects were borderline higher than those of MO subjects. These differences were attenuated with multivariable adjustment. For women there were no statistically significant differences between the groups. Multivariate-adjusted values were similar among groups, ranging from 0.70 to 0.83 mg/l for men and 0.85 to 0.87 mg/l for women.

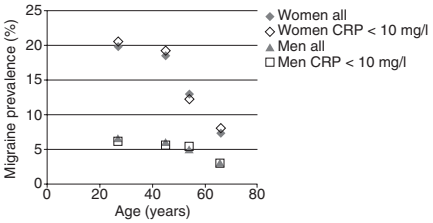

Figure 1 Comparing the age- and sex-specific 1-year prevalence of migraine between those with C-reactive protein (CRP) measurements ($n = 7251$) used in the current study and the entire cohort ($n = 21049$) of the Reykjavik Study and the Reykjavik Study for the Young.

Table 3 shows a comparison similar to that in Table 2, but with the stricter migraine criteria. The CRP values are almost identical for migraine defined with strict and relaxed criteria.

Table 4 shows age- and multivariate-adjusted CRP levels by age. Adjusted CRP levels increased gradually with age. In men CRP levels were consistently lower for MO subjects, compared with non-migraineurs and MA, but the difference was not significant. In women non-migraineurs and women with migraine and aura, there was a gradual increase in CRP levels with age. Women with MO had higher multivariable-adjusted CRP values in the young cohort, age group 19–34 years (1.01 mg/l for MO vs. 0.81 mg/l for non-migraineurs, $P = 0.08$), but with increasing age the CRP levels for women migraineurs with no aura gradually decreased, and by age 60–81 years CRP levels were significantly lower compared with migraineurs with aura and non-migraineurs (0.52 mg/l MO vs. 1.01 mg/l MA, $P = 0.029$; 0.52 mg/l MO vs. 1.07 mg/l control, $P = 0.007$).

Results with and without subjects who developed a coronary event during follow-up were similar. The difference in multivariable-adjusted CRP values after excluding those who were later

Table 1 Characteristics of subjects with C-reactive protein (CRP) measurements in the Reykjavik Study ($n = 5906$) and the Reykjavik Study for the Young ($n = 1345$) according to migraine* status

	Men young cohort			Men Reykjavik Study			Women young cohort			Women Reykjavik Study		
	No migraine	MO	MA	No migraine	MO	MA	No migraine	MO	MA	No migraine	MO	MA
Age, years (mean, S.D.)	27.8 (5.5)	27.2 (4.6)	28.6 (6.1)	54.1 (8.2)	53.0 (6.9)	51.6 (7.7)	27.6 (5.6)	26.8 (5.1)	29.0 (5.1)	58.0 (8.8)	54.1 (8.4)	54.9 (8.3)
BMI, kg/m^2 (mean, S.D.)	23.1 (2.8)	23.9 (3.5)	23.5 (2.5)	25.8 (3.5)	25.3 (3.0)	25.3 (3.1)	21.9 (2.8)	21.3 (2.9)	22.1 (4.0)	25.2 (4.4)	25.0 (4.6)	25.0 (4.1)
Cholesterol, mmol/l (mean, S.D.)	5.3 (1.0)	5.4 (1.1)	5.4 (1.1)	6.5 (1.1)	6.2 (0.9)	6.5 (1.2)	5.2 (0.9)	5.3 (0.9)	5.1 (0.8)	7.0 (1.3)	6.6 (1.0)	7.0 (1.2)
Diabetes (*n*, %)	1 (0.2)	0 (0)	0 (0)	185 (4.5)	3 (6.0)	5 (3.2)	0 (0)	0 (0)	0 (0)	74 (4.8)	0 (0)	8 (5.5)
CRP, mg/l (geometric mean, S.D.)†	0.59 (2.77)	0.54 (3.38)	0.69 (3.01)	1.31 (2.65)	0.98 (2.40)	1.23 (2.81)	0.78 (2.91)	0.90 (2.94)	0.75 (2.78)	1.22 (2.77)	0.81 (3.09)	1.19 (2.79)
Participants (*n*, %)	574 (100)	16 (100)	25 (100)	3977 (100)	50 (100)	150 (100)	584 (100)	71 (100)	75 (100)	1518 (100)	65 (100)	146 (100)
Headache	21.3	100	100	16.7	100	100	35.8	100	100	25.4	100	100
Pain, unilateral	6.3	87.5	56.0	4.7	84.0	63.0	9.2	77.5	69.3	6.2	80.0	70.5
Nausea/vomiting	0.5	50.0	32.0	0.8	66.0	37.0	1.9	53.5	57.3	2.4	76.9	62.3
Photophobia	1.9	87.5	76.0	0.8	66.0	53.9	5.1	87.3	69.3	1.3	58.5	60.3
Visual symptoms	0.7	0	96.0	1.1	0	78.6	1.7	0	85.3	1.3	0	83.6
Sensory symptoms	0	0	12.0	0.2	0	36.4	0.2	0	41.3	0.1	0	45.9
Elementary school or less education	17.8	6.3	24.0	36.8	46.0	48.7	18.2	19.7	18.7	65.4	50.8	68.5
Hypertension treatment	0.3	0	0	7.5	10.0	8.4	0.2	0	0	15.6	13.8	13.7
Current smoking	57.1	50.0	68.0	56.1	50.0	57.8	46.6	56.3	46.7	45.7	41.5	49.3
Former smoking	13.8	31.3	24.0	23.3	22.0	23.4	12.7	12.7	16.0	14.3	16.9	15.1
Medical hormone use	0	0	0	0.3	2.0	1.3	1.0	0	0	4.4	4.6	11.0
Contraceptive use							27.7	28.2	26.7	1.1	0	0.7

Values are percentages unless otherwise indicated.

*Migraine, relaxed criteria, defined as answering yes to two or more out of five questions on migraine.

†Subjects with CRP ≥ 10 mg/l were excluded.

MA, migraine with aura; MO, migraine without aura; BMI, body mass index.

[Correction added after online publication 20 May 2009: '—' was removed from columns 2–7 for the row 'Contraceptive use']

Table 2 Age- and multivariable-adjusted C-reactive protein (CRP) values (mg/l) with respect to migraine status, relaxed criteria* and gender

	No migraine	Migraine	*P*-vs. no migraine	MO	*P*-vs. no migraine	MA	*P*-vs. MO
Men	$n = 4551$	$n = 241$		$n = 66$		$n = 175$	
Age-adjusted model†	1.31 (1.27–1.35)	1.24 (1.09–1.40)	0.38	1.03 (0.81–1.31)	0.05	1.32 (1.14–1.53)	0.07
Multivariate-adjusted model‡	0.83 (0.77–0.90)	0.79 (0.69–0.91)	0.44	0.70 (0.54–0.89)	0.14	0.83 (0.71–0.97)	0.21
Women	$n = 2102$	$n = 357$		$n = 136$		$n = 221$	
Age-adjusted model†	1.17 (1.12–1.23)	1.14 (1.02–1.27)	0.63	1.09 (0.91–1.30)	0.42	1.17 (1.02–1.34)	0.51
Multivariate-adjusted model‡	0.87 (0.79–0.97)	0.87 (0.75–0.99)	0.90	0.85 (0.70–1.02)	0.75	0.87 (0.75–1.03)	0.75

*Migraine, relaxed criteria, defined as answering yes to two or more out of five questions on migraine.
†Subjects in the Reykjavik Study and the Reykjavik Study for the Young with available CRP measurements. CRP values ≥ 10 mg/l excluded.
‡CRP and migraine status in a linear regression model adjusted for case–control status, age, body mass index, cholesterol, smoking, education, hormone use, diabetes mellitus, systolic blood pressure (SBP) and antihypertensive therapy. For women adjustment was also made for birth control use. The profile used in the multivariable-adjusted model was: control with average values for continuous variables, non-smoker, high school education, SBP between 130 and 160 mmHg, without diabetes, hormone use and antihypertensive therapy. Women without birth control use.
All comparisons between MA and No migraine gave *P*-values > 0.8.
MA, migraine with aura; MO, migraine without aura.
[Correction added after online publication 20 May 2009: The table head of Table 2 has been corrected]

diagnosed with MI ranged from zero to 0.15 mg/l lower (0–19% decrease) for men and from being 0.14 mg/l higher to 0.05 mg/l lower (23% increase to 8% decrease) for women (data not shown).

Using 3 mg/l as a cut-off for elevated CRP levels, and excluding subjects with a history of MI, oral contraceptives and other medical hormone use, the proportion of men and women with elevated CRP was similar among subjects with and without migraine (19.3 and 20.0% for men and 14.1 and 16.6% for women). When stratifying by migraine aura, the proportions of non-migraineurs, MO and MA with elevated CRP were 20.0, 13.8 and 21.4% for men ($P = 0.43$, logistic regression with age adjustment) and 16.6, 9.7 and 16.8% for women ($P = 0.43$).

Discussion

In this nested case–control study, age-specific analysis of serum CRP levels was performed in subjects from two large cohort studies. Differences in CRP values between migraineurs and those without migraine were not significant, regardless of using linear regression with log-transformed CRP levels as a continuous variable or logistic regression with CRP as a binary variable. There was a moderate negative association between CRP levels and age among women with MO.

Inflammatory mechanisms have been involved in recent years and conceptualized in the neurogenic inflammation theory postulated by Waeber and Moskowitz (15). This theory accounts for the clinical efficacy of non-steroidal anti-inflammatory drugs and other anti-inflammatory drugs in aborting migraine attacks. Furthermore, inflammation being an important factor in atherogenesis and atherothrombosis, the association of migraine, especially MA, with stroke could be based on vascular inflammation as a link. The inference that inflammation is an important component in subsets of migraineurs has been further supported by the recent findings that the inflammatory marker, CRP, may be elevated in migraineurs (2, 5, 6). However, in all of those studies the elevation of CRP was modest at most and restricted to migraineurs without aura, a group that has not been generally found to be at increased risk of stroke (3, 16, 17). The principal finding of the present study is that CRP levels were not elevated among migraine sufferers compared with non-migraineurs. Nevertheless, certain subtleties require further consideration.

The multivariable-adjusted values in the Reykjavik Study were fairly low because they reflected subjects with a low cardiovascular disease risk

Table 3 Age- and multivariable-adjusted C-reactive protein (CRP) values (mg/l) with respect to migraine status and gender, using strict migraine criteria*

	No migraine	Migraine*	*P*
Men	*n* = 4551	*n* = 92	
Age-adjusted model†	1.30 (1.27–1.35)	1.23 (1.01–1.50)	0.58
Multivariable-adjusted model‡	0.83 (0.77–0.90)	0.79 (0.64–0.97)	0.59
Women	*n* = 2102	*n* = 180	
Age-adjusted model†	1.16 (1.11–1.22)	1.09 (0.94–1.27)	0.43
Multivariable-adjusted model‡	0.87 (0.79–0.97)	0.87 (0.73–1.03)	0.95

*Migraine, strict criteria: answering yes to three or more out of five questions on migraine.

†Subjects in the Reykjavik Study and the Reykjavik Study for the Young with available CRP measurements. CRP values ≥ 10 mg/l excluded.

‡CRP and migraine status in a linear regression model, adjusted for case–control status, age, body mass index, cholesterol, smoking, education, hormone use, diabetes mellitus, systolic blood pressure (SBP) and antihypertensive therapy. For women adjustment was also made for birth control use. The profile used in the multivariable-adjusted model was: control with average values for continuous variables, non-smoker, high school education, SBP between 130 and 160 mmHg, without: diabetes, hormone use and antihypertensive therapy. Women without birth control use.

profile. Age-adjusted CRP levels among men with MO were borderline lower than those of non-migraineurs and also borderline lower than those of migraineurs with aura, but after multivariate adjustment the differences between these groups were smaller and not statistically significant. CRP levels among migraineurs with aura and non-migraineurs were similar in all age categories for both men and women.

The association between migraine status, CRP and age seemed to be more complex in women than in men. Women with MO had slightly higher multivariable-adjusted CRP values in the age group 19–34 years. With increasing age the CRP level for women without aura fell and became significantly lower than that of non-migraineurs in the age group 60–81 years. Results for women in the age group 19–34 years are similar to those published by Vanmolkot and de Hoon (5). In their study 78% of participants were women, and the mean age was 25 years. The median CRP of those with MO was 2.11 mg/l, compared with 0.90 mg/l in controls ($P = 0.0002$). In a cohort study of women (mean age 55 years), the multivariable-adjusted prevalence odds ratio of having CRP > 4.2 mg/l was 1.14 (95% CI 1.02, 1.27) for active MO and 1.10 (95% CI 0.97, 1.26) for active MA vs. 1.00 for no history of migraine as control (6). This cohort study also showed a slight positive association between the attack frequency and the odds of having elevated CRP (6). Although it is clearly established that the prevalence of migraine is lower in older adults compared with middle-aged adults, it is not clear whether average attack frequency decreases with age. For example, Bigal et al. showed that the proportion of migraineurs with 10–14 headache days per month increased with age, and the attacks were less typical in elderly individuals (18), and Prencipe et al. have shown a similar attack frequency with increasing age among elderly migraineurs (19). In light of current knowledge on changes in attack frequency with age, it is not evident what effect age could have on CRP values among different age groups of migraineurs. Headache frequency was not estimated in the Reykjavik Study, so this question cannot be addressed.

In the present study, although not statistically significant, multivariable-adjusted CRP levels were generally higher in migraineurs with aura compared with migraineurs without aura, and this contradicts the results in the retrospective study of Welch and co-workers (2), the case–control study of Vanmolkot and de Hoon (5) and the cohort study of Kurth et al. (6).

The data in the current analysis from the Reykjavik Study were selected on the basis of availability of CRP measurements. The CRP measurements were part of a nested case–control study, thus raising the possibility of selection bias. However, we note that the age-specific prevalence of migraine in the sub-cohort used was almost identical to the prevalence within the entire cohort, which was randomly selected. This suggests that selection bias with regard to the presence of migraine is not more prevalent in the sub-cohort than in the entire cohort of > 21 000 subjects (8). Due to the selection criteria, there is probably an overrepresentation of cases with pre-existing coronary heart disease in the

Table 4 Age- and multivariable-adjusted C-reactive protein (CRP) values (mg/l) and migraine status relaxed criteria for men and women the Reykjavik Study and Reykjavik Study for the young

Cohort	Average age and range	Migraine status	*n*	Age-adjusted CRP (95% CI)	Migr. vs. no migr.	MO vs. MA	MO vs. no migr.	Multivariable-adjusted CRP (95% CI)	Migr. vs. no migr.	MO vs. MA	MO vs. no migr.
Men											
Reykjavik young	27	No migr.	513	0.57 (0.52, 0.63)				0.61 (0.49, 0.76)			
	19–34	Migraine	34	0.66 (0.46, 0.93)	$P = 0.47$			0.68 (0.45, 1.01)	$P = 0.55$		
		MO	13	0.50 (0.28, 0.89)		$P = 0.24$	$P = 0.64$	0.51 (0.28, 0.92)		$P = 0.19$	$P = 0.51$
		MA	21	0.77 (0.49, 1.21)				0.82 (0.50, 1.35)			
Reykjavik	44	No migr.	1168	1.14 (1.08, 1.21)				0.71 (0.61, 0.83)			
	35–49	Migraine	66	1.09 (0.87, 1.38)	$P = 0.72$			0.67 (0.51, 0.88)	$P = 0.63$		
		MO	11	1.01 (0.56, 1.82)		$P = 0.77$	$P = 0.68$	0.61 (0.34, 1.09)		$P = 0.70$	$P = 0.58$
		MA	55	1.11 (0.86, 1.44)				0.72 (0.56, 0.92)			
Reykjavik	54	No migr.	1856	1.30 (1.25, 1.36)				0.74 (0.66, 0.84)			
	50–59	Migraine	105	1.12 (0.93, 1.35)	$P = 0.12$			0.69 (0.56, 0.84)	$P = 0.26$		
		MO	32	0.93 (0.66, 1.32)		$P = 0.20$	$P = 0.06$	0.62 (0.44, 0.87)		$P = 0.44$	$P = 0.26$
		MA	73	1.21 (0.97, 1.52)				0.72 (0.56, 0.92)			
Reykjavik	66	No migr.	924	1.56 (1.47, 1.66)				1.16 (1.00, 1.36)			
	60–79	Migraine	27	1.61 (1.14, 2.28)	$P = 0.86$			1.26 (0.88, 1.82)	$P = 0.64$		
		MO	7	1.16 (0.57, 2.39)		$P = 0.30$	$P = 0.42$	0.93 (0.45, 1.90)		$P = 0.26$	$P = 0.55$
		MA	20	1.78 (1.19, 2.68)				1.50 (0.97, 2.31)			
Women											
Reykjavik young	27	No migr.	530	0.78 (0.71, 0.86)				0.81 (0.65, 1.01)			
	19–34	Migraine	137	0.80 (0.67, 0.96)	$P = 0.83$			0.87 (0.67, 1.13)	$P = 0.44$		
		MO	69	0.92 (0.71, 1.19)		$P = 0.13$	$P = 0.24$	1.01 (0.74, 1.37)		$P = 0.08$	$P = 0.08$
		MA	68	0.69 (0.53, 0.90)				0.75 (0.55, 1.02)			
Reykjavik	44	No migr.	236	0.94 (0.80, 1.09)				0.67 (0.50, 0.90)			
	35–49	Migraine	60	0.81 (0.61, 1.07)	$P = 0.35$			0.66 (0.46, 0.94)	$P = 0.96$		
		MO	21	0.72 (0.44, 1.16)		$P = 0.54$	$P = 0.24$	0.60 (0.36, 0.98)		$P = 0.56$	$P = 0.63$
		MA	39	0.86 (0.60, 1.22)				0.70 (0.46, 1.07)			
Reykjavik	54	No migr.	716	1.09 (1.01, 1.18)				0.73 (0.62, 0.87)			
	50–59	Migraine	101	1.11 (0.91, 1.36)	$P = 0.86$			0.78 (0.61, 0.99)	$P = 0.54$		
		MO	32	0.86 (0.60, 1.24)		$P = 0.09$	$P = 0.21$	0.66 (0.46, 0.96)		$P = 0.24$	$P = 0.55$
		MA	69	1.25 (0.98, 1.61)				0.85 (0.63, 1.13)			
Reykjavik	66	No migr.	564	1.52 (1.40, 1.64)				1.07 (0.87, 1.32)			
	60–81	Migraine	50	1.32 (1.02, 1.71)	$P = 0.31$			0.86 (0.63, 1.18)	$P = 0.11$		
		MO	12	0.87 (0.51, 1.49)		$P = 0.07$	$P = 0.04$	0.52 (0.30, 0.91)		$P = 0.03$	$P = 0.007$
		MA	38	1.51 (1.12, 2.04)				1.01 (0.71, 1.43)			

Migraine relaxed criteria defined as answering yes to two or more out of five questions on migraine. MA, migraine with aura; Migr., migraine; MO, migraine without aura. CRP, migraine status, age and gender in the Reykjavik Study and the Reykjavik Study for the Young using linear regression adjusting for case–control status, age, body mass index, cholesterol, smoking, education, hormone use, diabetes mellitus, systolic blood pressure (SBP) and antihypertensive use. Each age category was analysed separately and subjects with CRP values ≥ 10 mg/l were excluded. Profile used in multivariable adjusted model was: control with average values for continuous variables, non-smoker, high school education, SBP between 130 and 160 mmHg, without: diabetes, hormone use and antihypertensive therapy. Women without birth control use.

current study. When those who did not have a major coronary event during follow-up were analysed separately, CRP values were similar to those based on all cases. This indicates that the association between CRP values and migraine status is not different among subjects with coronary heart disease.

The questions in our study covered the most common migraine symptoms but did not include all of those identified in the 1988 IHS criteria (13). This is a cross-sectional analysis and cannot account for within-individual changes in CRP values. Furthermore, cross-sectional analysis cannot be used to determine any temporal relationship between CRP levels and the onset of migraine. Subjects entered the study from 1967 to 1991, resulting in a long period of sampling and analysis. However, a study of CRP and cardiovascular disease in subjects from the Reykjavik Study showed that the decade-to-decade consistency of CRP values was good (9). Alcohol use was not measured in the current study. Migraineurs have been reported to be less likely to consume alcohol than non-migraineurs (20), and alcohol is associated with a decrease in CRP levels (21, 22). Therefore, alcohol use is a potential confounder that cannot be adjusted for in the current study.

In the present study, contraceptive use among women resulted in a two- to threefold increase in CRP values (data not shown). Fröhlich et al. found that CRP levels among 844 women, in the MONICA Augsburg survey, aged 25–44 years, were 0.81 mg/l among non-users of oral contraceptives and 2.59 mg/l among oral contraceptive users (14). Our results for women without migraine are similar when multivariable adjustment (including oral contraceptive use) is applied (Tables 2 and 4).

In the present study migraine aura symptoms were more prevalent than expected, relative to MO symptoms (Table 4). Previous results suggest the proportion of migraineurs with aura symptoms to be 31% (20). A population-based study in the Netherlands (GEM Study) of 6491 adults aged 20–65 years reported the 1-year prevalence of migraine to be 25% for women and 7.5% for men (23). By combining MA and migraineurs both with and without aura in the GEM Study, the prevalence of MA, MO and unspecified migraine would be 7.5, 16 and 1.3%, respectively, for women and 2.3, 4.8 and 0.4% for men. In the present study the prevalence of MA and MO for women was 8.8 and 5.5%, and the prevalence for men was 3.6 and 1.3%. Comparing the prevalence in the Reykjavik Study and the GEM studies suggests that the prevalence of MA in the Reykjavik study is consistent with prior results, but the prevalence of MO may be underrepresented. One possible explanation could be recall bias when asked about headache symptoms, especially among milder migraine cases. This has been postulated by Liew et al., who found a higher lifetime prevalence of MA than MO among migraineurs in a population-based study of older men and women (24).

There is also potential misclassification of MO subjects as MA subjects, as some MO subjects experience non-specific visual disturbances during headaches, and the questions used do not distinguish between visual disturbances during the pain and before it starts. The effect of this misclassification might have been to attenuate or obscure possible differences in CRP levels between migraineurs with and without aura.

The questions on migraine symptoms in the Reykjavik Study did not allow for identifying subjects with cluster headache and chronic paroxysmal hemicranias, and these subjects were probably included with the migraineurs. Two studies by Remahl et al. did not show a difference in CRP values between subjects with cluster headache and subjects without headache, but these studies had few subjects (27 and 21 cases of cluster headache) and thus lacked the power to detect small differences (25, 26). The estimated prevalence of cluster headache and chronic paroxysmal hemicranias combined is < 0.5% (27, 28) and is therefore unlikely to affect our results to a great extent.

Information on the use of aspirin and statins was not recorded in this study, and both drugs can alter CRP values. However, we note that the use of these drugs was uncommon in the general population of Reykjavik between 1967 and 1991.

In conclusion, CRP levels were not increased among migraine sufferers compared with non-migraineurs. Migraineurs without aura tended to have lower CRP values than non-migraineurs and migraineurs with aura, except for young women migraineurs without aura, who had borderline higher CRP levels compared with migraineurs with aura and non-migraineurs. The association between CRP and migraine status was similar among those developing coronary heart disease during follow-up and those who did not.

Competing interests

None to declare.

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Paper III

Migraine Headache in Middle Age and Late-Life Brain Infarcts

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ORIGINAL CONTRIBUTION

Migraine Headache in Middle Age and Late-Life Brain Infarcts

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Context Migraine is considered to be an episodic condition with no long-term consequences. However, recent studies suggest that migraine attacks may be associated with pathologic changes in the brain, particularly in the cerebellum.

Objective To determine whether individuals not reporting headache compared with individuals reporting migraine symptoms, particularly aura, in midlife are at increased risk of late-life infarct-like lesions found on magnetic resonance imaging (MRI) without consideration of clinical symptoms.

Design, Setting, and Participants A population-based study of men and women in Reykjavik, Iceland (cohort born 1907-1935; n=4689; 57% women) were followed up since 1967, examined, and interviewed about migraine symptoms in midlife (mean age, 51 years; range, 33-65 years). Between 2002 and 2006, more than 26 years later, brain MRIs were performed. Participants reporting headaches once or more per month were asked about migraine symptoms including nausea, unilateral location, photophobia, visual disturbance, and numbness. These individuals with headache were classified as having migraine without aura, migraine with aura, or nonmigraine headache. A comprehensive cardiovascular risk assessment was performed at both examinations.

Main Outcome Measure Presence of infarct-like lesions (total) and specifically located in the cortical, subcortical, and cerebellar regions.

Results Infarct-like lesions were present in 39.3% of men and 24.6% of women. After adjusting for age, sex, and follow-up time, compared with those not reporting headaches once or more per month (n=3243), those with midlife migraine with aura (n=361) had an increased risk of late-life infarct-like lesions (adjusted odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1-1.8) that specifically reflected an association with cerebellar lesions in women (prevalence of infarcts 23.0% for women with migraine with aura vs 14.5% for women not reporting headaches; adjusted OR, 1.9; 95% CI, 1.4-2.6 vs a 19.3% prevalence of infarcts for men with migraine with aura vs 21.3% for men not reporting headaches; adjusted OR, 1.0; 95% CI, 0.6-1.8; $P<.04$ for interaction by sex). Migraine without aura and nonmigraine headache were not associated with an increased risk.

Conclusions Migraine with aura in midlife was associated with late-life prevalence of cerebellar infarct-like lesions on MRI. This association was statistically significant only for women. This is consistent with the hypothesis that migraine with aura in midlife is associated with late-life vascular disease in the cerebellum and in women.

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MIGRAINE, A COMMON NEUrovascular disorder that affects approximately 11% of adults and 5% of children worldwide, is more common in women than men and is most prevalent in the third and fourth decades of life.[1] Although a severe migraine attack is among the most disabling of neurological disorders,[2] many individuals with migraine do not consult physicians.[3]

Approximately one-third of individuals with migraine experience neurological aura symptoms before headache onset (migraine with aura), usually consisting of transient visual, and also sensory, aphasic, or motor disturbances.[4] Recent evidence suggests that migraine with aura is associated with an increased risk of clinically evident stroke or coronary artery disease.[5-9]

Migraine has also been linked to silent infarct-like lesions (identified on magnetic resonance imaging [MRI] regardless of clinical manifestations) in a community-based cohort evaluated as a part of the CAMERA study,[10] which showed that individuals with migraine had a 7-fold increased risk for infarcts in the cerebellum compared with controls, an association that was strongest in those with aura and frequent attacks (at least monthly).

See also p 2594 and Patient Page.

Although the precise etiology linking migraine with aura and vascular disease is uncertain,[5,6,11] the degree to which migraine is a marker or risk factor for brain changes that may have

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functional consequences in old age is a question of public health importance. We had the opportunity to study the relationship of midlife migraine symptoms and late-life infarct-like lesions (hereafter called infarcts) evident on MRI. The study is based on a large population-based cohort of men and women who have been followed up first as part of the Reykjavik Study and later as part of the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-RS).[12,13] We examined risk in men and women for infarcts in specific regions of the brain, and secondarily considered whether the risk varied by age at headache assessment and other established risk factors for vascular disease.

METHODS

Study Design

Detailed descriptions of the Reykjavik Study[12,14] and AGES-Reykjavik Study[13,15] have been published previously. In brief, the Reykjavik Study is a population-based cohort study established in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland.[12] The cohort included a random sample of men and women born between 1907 and 1935 and living in Reykjavik at baseline. In 2002, the Reykjavik Study continued as the AGES-Reykjavik Study to examine risk factors, genetic susceptibility, and gene-environment interactions in relation to disease and disability in old age.[13] Of the 11 549 (58% women) surviving members of the Reykjavik cohort (representing 64% of the original examined cohort), 8030 (68.6% of men and 70.1% of women) were randomly selected and invited to participate in the AGES-Reykjavik Study. Of these individuals, 71.8% participated (74.0% of men and 70.2% of women), deriving a final sample of 5764 (58% women). Participants had a slightly better cardiovascular risk profile (lower midlife cholesterol, systolic blood pressure, and fewer smokers). Recruitment details and comparisons of the AGES-Reykjavik Study with the original cohort have been described.[13]

We refer to the assessments of relevance to this study from the Reykjavik Study as midlife assessments, and to those from the AGES-Reykjavik Study as late-life assessments. Midlife assessments included questions about headache, measurement of cardiovascular risk factors, and demographic characteristics. Late-life assessments included MRI of the brain, measurement of cardiovascular risk factors, and history of cardiovascular disease. The average year of the midlife assessment was 1978 with 90% occurring between 1972 and 1986. Late-life assessments (including MRI) were conducted from 2002 through 2006.

Midlife Assessments

Headache. Participants were asked about current headache symptoms as part of the Reykjavik Study.[16] Those reporting headache once or more per month were asked whether the headaches were accompanied by any of the following 5 features of migraine: nausea or vomiting, unilateral location, photophobia, visual disturbance during or preceding headache, and unilateral numbness preceding headache.

Demographic and Cardiovascular Factors. Cardiovascular risk assessment was performed at the midlife examination concurrently with the migraine assessment. The following variables were considered putative confounders or mediators: educational level (primary, secondary, college, university), self-reported current use of medication for hypertension, smoking history (never, former, current smoker), and history of diabetes, as well as measured body mass index, systolic blood pressure, total cholesterol, and fasting blood glucose.

Late-Life Assessments

Brain MRI Protocol. All eligible participants were offered a high-resolution brain MRI acquired on a study-dedicated 1.5-T Signa Twinspeed system (General Electric Medical Systems, Waukesha, Wisconsin). The image protocol consisted of the following pulse sequences: T1-weighted 1.5-mm slice thickness 3-dimensional spoiled gradient-echo sequence (echo time [TE], 8 milliseconds; repetition time [TR], 21 milliseconds; flip angle (FA), 30°; field of view [FOV], 240 mm; matrix, 256×256) and in addition, with 3-mm thick interleaved slices, a proton density (PD)/T2-weighted fast spin-echo (SE) sequence (TE1, 22 milliseconds; TE2, 90 milliseconds; TR, 3220 milliseconds; echo train length, 8; FA, 90°; FOV, 220 mm; matrix, 256×256), and a fluid-attenuated inversion recovery (FLAIR) sequence (TE, 100 milliseconds; TR, 8000 milliseconds; inversion time, 2000 milliseconds; FA, 90°; FOV, 220 mm; matrix, 256×256). All images were acquired to give full brain coverage and slices were angled parallel to the anterior-posterior commissure line to give reproducible image views in the oblique axial plane.

Image Analysis. Infarcts were evaluated based on the T2-weighted fast SE/PD images and FLAIR images.

Infarcts were defined based on radiologic characteristics as described. A parenchymal defect (infarct) was defined as a defect of the brain parenchyma with a signal intensity that is isointense to that of cerebrospinal fluid on all pulse sequences (ie, FLAIR, T2-weighted, PD-weighted). Cortical infarct-like lesions were defined as parenchymal defects involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images. Subcortical infarcts were defined as parenchymal defects not extending into the cortex that are surrounded by an area of high signal intensity on FLAIR images. Defects in the subcortical area without a rim or area of high signal intensity on FLAIR, and without evidence of hemosiderin on the T2*-weighted GRE-EPI scan were labeled as large Virchow-Robin Spaces (VRS); these were excluded from the definition of subcortical infarcts. Defects in the subcortical area with evidence of hemosiderin on the T2*-weighted GRE-EPI scan were labeled as resorbed hematomas and were also excluded from the definition of subcor-

tical infarcts. Lesions 4 mm or larger were recorded except for those in the cerebellum, for which there was no size criterion. Infarcts that spanned 2 areas were assigned to the location with the largest measured (mm) diameter of the defect regardless of orientation. This protocol was comparable with the protocol used in the CAMERA study.[10]

Image analyses were performed in a 2-step procedure by readers blinded to participant health status, including midlife headache history. An experienced neuroradiologist examined the scan for clinical abnormalities that needed immediate attention. At the same time, the neuroradiologist recorded the slice location of observed cortical and cerebellar infarcts directly into a shared database. Trained raters with access to the shared database identified subcortical infarcts and characterized all of the infarcts in more radiologic detail. Quality control procedures included 6 monthly assessments of intraobserver variability, and 3 monthly assessments for interobserver differences. The intraobserver weighted κ statistic was 0.92 for cerebral infarcts; the interobserver weighted κ statistic was 0.66 for cerebral infarcts. In addition, a 5% random sample was reread by a trained neuroradiologist at Leiden University Medical Center, Leiden, the Netherlands, and differences discussed.

Late-Life Cardiovascular Risk Factors and Disease. Late-life measurements included carotid artery distensibility by ultrasonography and coronary calcification (Agatston units) measured by computed tomography; both these measures were categorized into sex-specific quartiles. Diabetes was defined based on self-reported history of diabetes, use of medication, or fasting glucose levels greater than 126 mg/dL; systolic blood pressure was taken twice and averaged for the final measure; and standard questions were administered to assess smoking history (never, former, current) and history of physician diagnosis of stroke and transient ischemic attack (TIA). History of coronary artery disease (CAD) was defined as a self-reported physician diagnosis of myocardial infarction or angina, or a history of coronary angioplasty or coronary artery bypass graft with supporting evidence from electrocardiography or nitrate use.

Analytic Sample. Of the 5764 AGES-Reykjavik participants, 5003 underwent MRI. Reasons for nonparticipation included contraindications (n=280), refusal (n=283), or being examined via home visit rather than clinic (n=198). An additional 237 participants were not included in the analysis because of either not completing all image sequences needed for infarct assessment or insufficient scan quality for infarct assessment. We excluded an additional 77 individuals who were older than 65 years at the time of the midlife examination. The final analytic sample thus consists of 4689 surviving Reykjavik Study participants who had complete headache and MRI data. Those excluded were older (79 vs 76 years of age), had a higher midlife systolic blood pressure, and a higher prevalence of CAD, stroke, or TIA in late life ($P<.001$ for all). Sex or midlife migraine status did not differ between individuals who were included and excluded from these analyses.

Statistical Analyses. Based on the midlife headache questions, we classified participants into 4 mutually exclusive headache categories: No headache once or more per month (reference category), nonmigraine headache, migraine without aura, and migraine with aura. The migraine without aura category included individuals with headache with at least 2 of the 3 nonaura symptoms (nausea, unilateral location, photophobia). The migraine with aura category included those reporting visual aura, sensory aura, or both. Individuals with headache but no nonaura symptoms or 1 nonaura symptom (nausea, unilateral location, or photophobia) were defined as having nonmigraine headache. Aura symptoms took precedence over other symptoms.

The classification scheme represents an approximation of International Headache Society diagnostic criteria for migraine with or without aura, which were formalized after the midlife data were collected.[17] International Headache Society features for migraine without aura that are missing from these criteria include pulsatility, exacerbation with activity, and phonophobia. International Headache Society criteria for migraine with aura missing from these criteria include duration of aura (aura symptoms must last between 5 and 60 minutes) and speed of onset (aura symptoms must develop gradually over more than 5 minutes). Due to the screening question for headache, our case definition does not include individuals who experience aura exclusively without headache.

A priori analyses were conducted for the total sample and stratified by sex. We used logistic regression to estimate the odds (95% confidence interval [CI]) of prevalent late-life infarcts in those with midlife migraine symptoms relative to individuals without midlife migraine symptoms. Separate models were calculated for cerebellar, cortical, subcortical, and total infarcts for the total sample and by sex. In model 1, we adjusted for age at the midlife examination, sex (for analyses on the total sample), and duration of follow-up. In model 2 we additionally adjusted for possible confounding by midlife cardiovascular factors. We tested for sex differences in the relationship between midlife migraine and late-life infarcts by including an interaction term in model 1 and model 2 (eg, migraine × sex).

In secondary analyses, we adjusted for late-life cardiovascular risk factors and stratified by a history of CAD or TIA/stroke, to examine whether the associations of migraine to infarcts were changed by these factors. We tested for interaction by the age at which migraine symptoms were assessed (age <50 years, age ≥50 years), CAD, and TIA/stroke history by including interaction terms as previously shown. All analyses were performed with Stata version 10.1 (StataCorp LP, College Station, Texas).

The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN-00-063), which acts as the institutional review board for the Icelandic Heart Association and by the institutional review board for the US National Institute on Aging, National Institutes of Health. Written informed consent was obtained from all participants.

RESULTS

Participants were 2693 women and 1996 men with an average age of 50.9 years (range, 33-65) at the midlife interview and 76.2 years (range, 66-96) at the late-life interview (TABLE 1). Overall, 12.2% of the participants (5.7% of men; 17.0% of women) were classified as having migraine, including 4.5% migraine without aura (1.5% of men; 6.6% of women) and 7.7% migraine with aura (4.2% of men; 10.3% of women). Among participants with aura, the proportion with visual aura, sensory aura, and both visual and sensory aura, respectively, was 77.1%, 14.5%, and 8.4% for men and 66.2%, 17.3%, and 16.5% for women. Within the mi-

Table 1. Characteristics of Participants by Midlife Migraine Status[a]

	No. of Men (n = 1996)[b]				No. of Women (n = 2693)[b]			
Headache Status	No Headache (n = 1589)[c]	Non-migraine Headache (n = 294)[d]	Migraine Without Aura (n = 30)[e]	Migraine With Aura (n = 83)[f]	No Headache (n = 1654)[c]	Non-migraine Headache (n = 582)[d]	Migraine Without Aura (n = 179)[e]	Migraine With Aura (n = 278)[f]
Age at midlife examination, mean (SD), y	49.9 (5.7)	49.3 (6.1)	48.3 (5.1)	47.6 (5.7)	52.5 (6.1)	50.7 (6.4)	49.2 (6.2)	50.5 (6.1)
Age at late-life examination, mean (SD), y	76.6 (5.3)	76.0 (5.4)	75.0 (3.9)	74.6 (4.9)	76.7 (5.4)	75.3 (5.2)	74.2 (4.8)	75.1 (5.3)
Follow-up time, mean (SD), y	26.7 (3.1)	26.6 (3.1)	26.7 (2.5)	27.0 (2.7)	24.2 (4.1)	24.6 (4.4)	25.0 (4.3)	24.7 (4.0)
Midlife interview 1, risk profile								
Primary education, No. (%)	358 (22.5)	71 (24.2)	5 (16.7)	24 (28.9)	710 (42.9)	244 (41.9)	69 (38.6)	122 (43.9)
Current smoking, No. (%)	724 (45.6)	131 (44.6)	12 (40.0)	42 (50.6)	532 (32.2)	171 (29.4)	40 (22.4)	87 (31.3)
Body mass index, mean (SD)[g]	25.5 (3.1)	25.4 (3.1)	25.5 (3.0)	25.9 (3.3)	24.8 (3.6)	25.0 (4.1)	24.9 (3.8)	24.7 (3.5)
Diabetes, No. (%)	11 (0.7)	4 (1.4)	0	1 (1.2)	14 (0.9)	1 (0.2)	3 (1.7)	6 (2.2)
Fasting glucose level, mean (SD), mg/dL	80.3 (10.0)	79.2 (9.5)	81.2 (8.7)	81.3 (21.9)	76.9 (9.1)	76.5 (9.1)	78.1 (14.7)	76.5 (10.6)
Antihypertensive medication use, No. (%)	57 (3.6)	13 (4.4)	1 (3.3)	4 (4.8)	115 (7.0)	57 (9.8)	11 (6.2)	24 (8.6)
Systolic blood pressure, mean (SD), mm Hg	135.2 (15.8)	134.3 (16.6)	131.4 (10.0)	132.4 (13.0)	129.2 (17.1)	130.6 (17.5)	130.8 (16.5)	126.4 (14.7)
Total cholesterol level, mean (SD), mg/dL	247.5 (38.7)	243.6 (38.7)	235.9 (31.0)	239.8 (38.7)	247.5 (42.5)	243.6 (46.4)	235.9 (42.5)	243.6 (46.4)
Late-life interview 2, risk profile								
Coronary calcification top quartile, No. (%)	387 (24.6)	70 (24.1)	9 (31.0)	24 (29.6)	421 (25.7)	125 (21.6)	26 (14.5)	60 (21.8)
Carotid artery distensibility (bottom quartile), No. (%)	385 (25.3)	70 (24.8)	5 (17.2)	25 (32.1)	398 (25.4)	121 (21.7)	58 (34.1)	55 (20.8)
Diabetes, No. (%)	235 (14.8)	39 (13.3)	6 (20.0)	16 (19.3)	141 (8.5)	53 (9.1)	23 (12.9)	25 (9.0)
Current smoking, No. (%)	260 (16.4)	46 (15.7)	6 (20.0)	17 (20.7)	209 (12.7)	69 (11.9)	19 (10.6)	41 (14.8)
Antihypertensive medication use, No. (%)	979 (61.6)	179 (60.9)	22 (73.3)	53 (63.9)	1007 (60.9)	385 (66.2)	122 (68.2)	190 (68.4)
Systolic blood pressure, mean (SD), mm Hg	143.0 (20.2)	143.5 (18.8)	142.0 (18.3)	145.6 (21.1)	141.8 (20.8)	141.4 (20.6)	144.1 (21.7)	140.0 (17.5)
History of coronary artery disease, No. (%)	558 (39.7)	112 (41.3)	16 (57.1)	38 (48.7)	313 (20.7)	130 (23.9)	37 (21.9)	83 (31.3)
History of stroke or transient ischemic attack, No. (%)	144 (9.4)	33 (11.5)	6 (20.0)	7 (9.0)	100 (6.2)	37 (6.5)	8 (4.6)	26 (9.8)

SI conversions; To convert glucose to mmol/L, multiply by 0.0555; cholesterol to mmol/L, divide by 0.02586.
[a] From the AGES-Reykjavik study.
[b] Migraine symptoms asked of individuals reporting headache once or more per month included photophobia, nausea, unilateral location, visual disturbance during or just before headache, and unilateral numbness during or just before headache. Four categories of headache symptoms are mutually exclusive.
[c] No headache: does not have headache once or more per month.
[d] Nonmigraine headache: headache with no more than 1 associated symptom.
[e] Migraine without aura: headache with 2 or 3 associated symptoms of photophobia, nausea, or unilateral location. Individuals with aura and nonaura symptoms are included in the aura category.
[f] Migraine with aura: headache with visual aura, sensory aura, or both. Individuals with aura and nonaura symptoms are included in the aura category.
[g] Body mass index calculated as weight in kilograms divided by height in meters squared.

graine with aura group, 89% reported having at least 1 other migraine symptom.

Individuals with migraine were slightly younger at the midlife examination compared with others (Table 1). Other differences were that women with migraine with aura were more likely to report a history of CAD or TIA/stroke than those without ($P<.005$), although most other measures of cardiovascular risk were not obviously different.

Infarcts were present on MRI in 39.3% of men and 24.6% of women. The most common lesion location was the cerebellum (21.0% in men and 14.7% in women; TABLE 2).

Table 2. Prevalence of Late-Life Infarct-Like Lesion by Midlife Migraine Status: AGES-Reykjavik Study

	No. With Status/No. With Infarct (%)			
	Cerebellar	Cortical	Subcortical	Total
Men				
No headache	1589/339 (21.3)	1573/244 (15.5)	1573/262 (16.7)	1589/621 (39.1)
Nonmigraine headache	294/61 (20.8)	291/52 (17.9)	291/42 (14.4)	294/118 (40.1)
Migraine without aura	30/3 (10.0)	30/7 (23.3)	30/5 (16.7)	30/12 (40.0)
Migraine with aura	83/16 (19.3)	83/15 (18.1)	83/11 (13.3)	83/34 (41.0)
Total	**1996/419** (21.0)	**1977/318** (16.1)	**1977/320** (16.2)	**1996/785** (39.3)
Women				
No headache	1654/240 (14.5)	1642/131 (8.0)	1642/138 (8.4)	1654/415 (25.1)
Nonmigraine headache	582/66 (11.3)	578/35 (6.1)	578/43 (7.4)	582/125 (21.5)
Migraine without aura	179/26 (14.5)	178/7 (3.9)	178/10 (5.6)	179/36 (20.1)
Migraine with aura	278/64 (23.0)	278/23 (8.3)	278/20 (7.2)	278/86 (30.9)
Total	**2693/396** (14.7)	**2675/196** (7.3)	**2675/211** (7.9)	**2693/662** (24.6)

Primary Results

In unadjusted comparisons, infarcts overall were more prevalent in women with migraine with aura compared with women without headache (31% vs 25%; $P=.04$; Table 2) but there was no difference in prevalence for men (41% vs 39%). Infarcts in the cerebellum, but not in other locations, were more prevalent in women with migraine with aura compared with women without headache (23% vs 15%; $P<.001$); there was no difference in prevalence for men (19% vs 21%).

After adjusting for age, sex, and follow-up time in a pooled model for men and women, participants with midlife migraine with aura were at increased risk for total infarcts (adjusted odds ratio [OR], 1.4; 95% CI, 1.1-1.8; TABLE 3). This mainly reflects the risk associated with lesions located in the cerebellum (adjusted OR, 1.6; 95% CI, 1.3-2.2; Table 3). There was no increased risk for cortical or subcortical lesions (Table 3) for participants with midlife migraine with aura, migraine without aura, or nonmigraine headache. Results were similar without (model 1) or after (model 2) adjustment for midlife measures of cardiovascular risk.

The relationship between migraine with aura and cerebellar infarcts was only significant in women (men, adjusted OR, 1.0; 95% CI, 0.6-1.8 vs women, adjusted OR, 1.9; 95% CI, 1.4-2.6; $P=.04$ for interaction by sex; Table 3), but was not statistically different by the age at which headache symptoms were assessed (age <50 years, adjusted OR, 2.0; 95% CI, 1.4-3.0 vs age ≥50 years, adjusted OR, 1.4; 95% CI, 0.9-2.0; $P=.18$ for interaction by age, TABLE 4).

For cortical infarcts in the migraine without aura group, there was an interaction by sex, suggesting a higher risk in men compared with women ($P=.04$), although the individual sex-stratified ORs were not significant (Table 4). Results were generally similar when stratified by age (Table 4), although there was also a marginally increased risk for cortical infarcts in participants aged ≥50 years with migraine with aura (adjusted OR, 1.6; 95% CI, 1.0-2.5; $P=.07$).

Secondary Analyses

Results were similar after adjusting for late-life measures of cardiovascular risk and history of CAD or TIA/stroke. The relationship between migraine with aura and cerebellar infarcts was not changed by adjustment for late-life measures of cardiovascular risk and history of CAD or TIA/stroke in the total sample (adjusted OR, 1.5; 95% CI, 1.2-2.0) or when analyzed separately for men (adjusted OR, 1.0; 95% CI, 0.5-1.7) and women (adjusted OR, 1.8; 95% CI, 1.3-2.5). The association did not differ by CAD history (interaction, $P<.13$) with no CAD history having an adjusted OR of 1.8 (95% CI, 1.2-2.5) and with CAD history having an adjusted OR of 1.2 (95% CI, 0.8-1.9). The relationship did not differ by history of TIA or stroke (no history, adjusted OR, 1.7; 95% CI, 1.2-2.3; vs with history, adjusted OR, 1.6; 95% CI, 0.8-3.5; $P=.57$ for interaction by TIA/stroke history).

The separate analyses of visual and sensory aura symptoms suggested that the association of cerebellar infarcts with migraine with aura in women was stronger in those (8.6% of all women) with visual aura (adjusted OR, 2.2; 95% CI, 1.5-3.1) compared with those (1.7% of all women) with only sensory aura symptoms (adjusted OR, 1.3; 95% CI, 0.6-2.8).

COMMENT

In a large cohort of Icelandic adults, we found that women who reported migraine with aura in middle age were at increased risk of late-life infarcts relative to those without migraine symptoms. The risk was primarily for cerebellar lesions; there was no increased risk for cortical or subcortical lesions in these women or for those with migraine without aura or nonmigraine headache.

This risk was independent of cardiovascular risk factors measured in midlife or late life. Risk was not statistically different between individuals who were aged 50 years or younger vs those who were older when headache was ascer-

tained or between those with a history of diagnosed CAD or TIA/stroke vs those without.

Our study has substantial strengths. The large well-characterized cohort was established in 1967 when, at the time of headache assessment, participants were aged 33 to 65 years. At those ages, many participants were still experiencing migraines, therefore recall bias is likely reduced. Participants were also at low risk for TIA or stroke, making the identification of migraine visual aura symptoms more robust. Measurement of late-life infarcts on MRI was performed by raters blinded to midlife headache status. Because participants were followed up as part of a cardiovascular disease study, we were also able to rigorously adjust for plausible confounding cardiovascular risk factors. Other strengths include the size of our cohort and broad age range, which gave us statistical power to consider sex, age, and cardiovascular disease in our analyses.

Some limitations of this study should be taken into account when interpreting the findings. Because migraine symptom questions were not asked of those reporting headache less than once per month, we are likely capturing only those with severe migraine occurring with a higher frequency. Participants with aura only and no headache would be classified as having no migraine. Further, our assessment of migraine was based on pre-IHS diagnostic criteria, although the questions addressed 5 symp-

Table 3. Adjusted Odds of Late-Life Infarct-Like Lesions by Midlife Migraine Status, Overall and Sex-Stratified: AGES-Reykjavik Study

	Odds Ratio (95% Confidence Interval)							
	Cerebellar		Cortical		Subcortical		Total Infarcts	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Total								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	0.9 (0.7-1.1)	0.9 (0.7-1.1)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Migraine without aura	1.0 (0.7-1.5)	1.0 (0.7-1.5)	0.9 (0.5-1.5)[c]	0.9 (0.5-1.6)[c]	0.8 (0.5-1.4)	0.9 (0.5-1.5)	0.9 (0.7-1.3)	1.0 (0.7-1.4)
Migraine with aura	1.6 (1.3-2.2)[c]	1.7 (1.3-2.2)[c]	1.3 (0.9-1.8)	1.3 (0.9-1.9)	0.9 (0.6-1.3)	0.9 (0.6-1.4)	1.4 (1.1-1.8)	1.5 (1.2-1.9)
Men								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	1.0 (0.7-1.4)	1.0 (0.7-1.4)	1.2 (0.9-1.7)	1.3 (0.9-1.8)	0.9 (0.6-1.2)	0.9 (0.6-1.2)	1.1 (0.8-1.4)	1.1 (0.9-1.4)
Migraine without aura	0.5 (0.1-1.5)	0.5 (0.2-1.7)	1.8 (0.8-4.3)	2.0 (0.8-4.8)	1.1 (0.4-2.9)	1.1 (0.4-3.0)	1.2 (0.6-2.5)	1.3 (0.6-2.7)
Migraine with aura	1.0 (0.6-1.8)	1.0 (0.6-1.8)	1.3 (0.7-2.4)	1.4 (0.8-2.6)	0.9 (0.4-1.6)	0.8 (0.4-1.6)	1.3 (0.8-2.0)	1.3 (0.8-2.0)
Women								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.8 (0.6-1.2)	0.8 (0.6-1.2)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Migraine without aura	1.1 (0.7-1.8)	1.1 (0.7-1.8)	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.8 (0.4-1.5)	0.9 (0.4-1.7)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
Migraine with aura	1.9 (1.4-2.6)	2.0 (1.4-2.7)	1.2 (0.7-1.9)	1.2 (0.7-1.9)	0.9 (0.6-1.5)	1.0 (0.6-1.7)	1.5 (1.1-2.0)	1.5 (1.2-2.1)

[a] Model 1: adjusted for age at midlife examination, sex, and duration of follow-up.
[b] Model 2 (includes model 1 adjustments): adjusted for midlife systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index (calculated as weight in kilograms divided by height in meters squared), use of medication for hypertension, smoking history, and diabetes.
[c] Significant (P <.05) interaction by sex for cerebellar and cortical infarcts.

Table 4. Adjusted Odds of Late-Life Infarct-Like Lesions by Midlife Migraine Status, Stratified by Age at Midlife Interview: AGES-Reykjavik Study[a]

	Odds Ratio (95% Confidence Interval)							
	Cerebellar		Cortical		Subcortical		Total Infarcts	
	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]
Age <50 y								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.0 (0.7-1.5)	1.0 (0.7-1.5)	0.9 (0.6-1.3)	0.9 (0.6-1.3)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
Migraine without aura	1.4 (0.9-2.4)	1.4 (0.8-2.5)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.7 (0.3-1.6)	0.7 (0.3-1.6)	1.2 (0.8-1.9)	1.2 (0.8-1.9)
Migraine with aura	2.0 (1.4-3.0)	2.1 (1.4-3.1)	1.0 (0.6-1.8)	1.1 (0.6-2.0)	0.7 (0.4-1.3)	0.7 (0.4-1.3)	1.5 (1.1-2.1)	1.5 (1.1-2.2)
Age ≥50 y								
No headache	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Nonmigraine headache	0.8 (0.6-1.0)	0.8 (0.6-1.0)	1.1 (0.8-1.5)	1.1 (0.8-1.5)	0.9 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.1)	0.9 (0.7-1.2)
Migraine without aura	0.6 (0.3-1.3)	0.6 (0.3-1.3)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.9 (0.4-2.0)	1.1 (0.5-2.4)	0.7 (0.4-1.2)	0.8 (0.4-1.3)
Migraine with aura	1.4 (0.9-2.0)	1.4 (0.9-2.1)	1.6 (1.0-2.5)	1.6 (1.0-2.6)	1.1 (0.7-1.9)	1.2 (0.7-2.0)	1.4 (1.0-2.0)	1.5 (1.1-2.1)

[a] No significant (P <.05) interaction by age.
[b] Model 1: adjusted for age at midlife examination, sex, and duration of follow-up.
[c] Model 2 (includes model 1 adjustments): adjusted for midlife systolic blood pressure, total cholesterol, fasting blood glucose, educational level, body mass index (calculated as weight in kilograms divided by height in meters squared), use of medication for hypertension, smoking history, and diabetes.

toms included in the IHS guidelines. We note that our estimated prevalence of migraine overall (eg, with or without aura) is highly consistent with prior studies.[1] Our prevalence of aura (as a proportion of the total migraine population) is higher than has been reported in other population studies and may include frequently occurring nonspecific visual symptoms such as blurring. However, the likely effect of this misclassification would be to attenuate the relationship between migraine with aura and infarcts, unless, compared with aura, nonspecific symptoms are differentially more strongly related to the risk for infarcts, a hypothesis we believe is unlikely.

Given the age of our study population, it is worth considering the extent to which overall or cardiovascular-related mortality may have affected our results. In particular, those with migraine with aura have been reported to be at increased risk of cardiovascular death compared with others.[7] If individuals with midlife migraine with aura were more likely to die of cardiovascular disease before the late-life examination, and if these individuals were also more likely to have infarcts in the cerebellum or overall compared with others, then our results would have been attenuated. However, if these cerebellar or overall lesions were somehow protective (eg, individuals with migraine with aura and these lesions had lower all-cause mortality compared with those with migraine with aura without these lesions), then our results would have been exaggerated. The second scenario seems unlikely.

Our results are consistent with the cross-sectional CAMERA study,[10] the only other study that measured infarcts on MRI, which also found the migraine-associated infarcts to be preferentially located in the cerebellum. This prospective longitudinal study had a long follow-up and an older cohort with a much higher background risk for brain lesions. Our results suggest that the association of infarcts with migraine with aura is detectable in older individuals who typically have cardiovascular risk factors that lead to similar-appearing lesions.[18] Further, the study is based on a larger sample of men and women, therefore, sex differences could be investigated. We found that the relationship between migraine with aura and cerebellar infarcts may be specific to women. However, we cannot rule out a possible increased risk for men with migraine with aura due to the relatively small number of men with migraine with aura in our sample.

Why migraine, particularly with aura, is associated with clinical and silent (presumed) ischemic stroke is uncertain. Proposed mechanisms include atherosclerotic and nonatherosclerotic causes,[5,6,11] including traditional cardiovascular risk factors,[11,19] endothelial dysfunction,[11,20-22] shared genetic risk factors for migraine and stroke,[11,23-25] vasoconstrictor medications taken to treat headache,[11,22] cardiac abnormalities including patent foramen ovale,[11,26] and diagnostic artifact,[11,27] among other factors. These mechanisms do not obviously explain why infarcts associated with migraine with aura would be preferentially located in the cerebellum and in women. There are clinical reports suggesting that the cerebellum is vulnerable in individuals with migraine[28-32] and in familial hemiplegic migraine—a rare Mendelian variant of migraine with aura.[33] In population studies, no particular location pattern was evident for clinically evident ischemic stroke among women with aura,[9,34] although as mentioned earlier, silent infarcts (as per the CAMERA study) were preferentially located in the cerebellum.[10] We also note that secondary analyses suggested an association of migraine with aura to cortical infarcts in some subgroups was stronger (eg, men with migraine with or without aura or men and women who were older than aged 50 years at the time of headache assessment).

In summary, this study suggests that a remote history of migraine with aura is associated with brain lesions commonly found in older populations. Results persisted after controlling for cardiovascular risk factors and history of cardiovascular disease, thus suggesting that the mechanism linking the migraine aura with these lesions is independent of the usual risk factors for ischemic vascular disease and may be specifically related to migraine with aura. Additional longitudinal studies with repeated MRIs are needed to better establish the temporality and dose-response relationship between migraine with aura and brain infarcts. Finally, the clinical implications of the infarct-like lesions identified have not been established and will require investigation.

Author Contributions: Dr Scher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Scher, Eiriksdottir, van Buchem, Gudnason, Launer.
Acquisition of data: Sigurdsson, Eiriksdottir, Gudnason.
Analysis and interpretation of data: Scher, Gudmundsson, Sigurdsson, Ghambaryan, Aspelund, van Buchem, Gudnason.
Drafting of the manuscript: Scher.
Critical revision of the manuscript for important intellectual content: Gudmundsson, Sigurdsson, Ghambaryan, Aspelund, van Buchem, Eiriksdottir, Gudnason, Launer.
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Paper IV

BMJ

RESEARCH

Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study

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ABSTRACT

Objective To estimate whether migraine in mid-life is associated with mortality from cardiovascular disease, other causes, and all causes.

Design Population based cohort study.

Setting Reykjavik, Iceland.

Participants 18 725 men and women, born 1907-35 and living in Reykjavik and adjacent communities.

Main outcome measures Mortality from cardiovascular disease, non-cardiovascular disease, and all causes. Questionnaires and clinical measures were obtained in mid-life (mean age 53, range 33-81) in the Reykjavik Study (1967-91). Headache was classified as migraine without aura, migraine with aura, or non-migraine headache. Median follow-up was 25.9 years (0.1-40.2 years), with 470 990 person years and 10 358 deaths: 4323 from cardiovascular disease and 6035 from other causes. We used Cox regression to estimate risk of death in those with migraine compared with others, after adjusting for baseline risk factors.

Results People with migraine with aura were at increased risk of all cause mortality (adjusted (for sex and multivariables) hazard ratio 1.21, 95% confidence interval 1.12 to 1.30) and mortality from cardiovascular disease (1.27, 1.13 to 1.43) compared with people with no headache, while those with migraine without aura and non-migraine headache were not. Further examination of mortality from cardiovascular disease shows that people with migraine with aura were at increased risk of mortality from coronary heart disease (1.28, 1.11 to 1.49) and stroke (1.40, 1.10 to 1.78). Women with migraine with aura were also at increased risk of mortality from non-cardiovascular disease (1.19, 1.06 to 1.35).

Conclusions Migraine with aura is an independent risk factor for cardiovascular and all cause mortality in men and women. The risk of mortality from coronary heart disease and stroke mortality is modestly increased in people with migraine, particularly those with aura.

INTRODUCTION

In recent years, numerous studies have suggested that migraine, particularly migraine with aura, is a risk factor for clinical and subclinical cardiovascular disease.[1-6] Both we and others have examined the relation between cardiovascular risk factors and migraine, showing differences in risk factors between those with and without migraine.[7-10] Less well understood is the degree, if any, to which migraine is related to the risk of all cause or cardiovascular mortality. Few articles have been published on migraine and cardiovascular disease or overall mortality, with somewhat conflicting findings, depicting migraine as a risk factor, neutral, or a protective factor.[4 6 11-14] Because of insufficient data, a recent meta-analysis could draw no conclusions regarding the risk of mortality associated with migraine with aura.[6] We estimated the risk of mortality from cardiovascular disease, non-cardiovascular disease, and all causes associated with having migraine with or without aura at mid-life during up to four decades of follow-up in a population based cohort.

METHODS

Study design

Detailed descriptions of the Reykjavik Study have previously been published.[15 16] In brief, the Reykjavik Study is a population based cohort study established in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland.[16] The cohort included a random sample of men and women born in 1907-35 and living in Reykjavik. The first examination of each person occurred between 1967 and 1991, the average year of examination was 1975 (see appendix 1 on bmj.com).

Headache assessment

Participants were asked about current headache symptoms.[8] Those reporting headache once or more a month were asked whether the headaches were accompanied by any of the following five features of migraine: nausea or vomiting, unilateral location, photophobia, visual disturbance during or preceding headache, and unilateral numbness preceding headache.

We classified participants into four mutually exclusive categories of headache: no headache once or more a month (reference category), non-migraine headache, migraine without aura, and migraine with aura. The category of migraine without aura included individuals with headache with at least two of the three non-aura

symptoms (nausea, unilateral location, photophobia). The category of migraine with aura included those who reported visual aura or sensory aura, or both. Individuals with headache but no non-aura symptoms or only one non-aura symptom were defined as having non-migraine headache. Aura symptoms took precedence over other symptoms. The classification scheme represents an approximation of the 2004 diagnostic criteria of the International Headache Society (IHS)[17] for migraine with or without aura, which were formalised after the Reykjavik Study data were collected. Features for migraine without aura that are missing from these IHS criteria include pulsatility, exacerbation with activity, and phonophobia. Criteria for migraine with aura missing from these criteria include duration of aura (aura symptoms must last between 5 and 60 minutes) and speed of onset (aura symptoms must develop gradually over more than 5 minutes).

Assessment of demographic and cardiovascular factors

Assessment of cardiovascular risk was performed at the same time as the migraine assessment. Nurses administered questionnaires, made physical measurements, performed spirometry and electrocardiography, and collected venous blood samples.

Endpoint definition

After entering the study, participants were followed for up to 40 years (until the end of 2007). Statistics relating to the cause of death, given by an ICD (international classification of disease) code, were obtained from Statistics Iceland. The main end points in our study were deaths from cardiovascular disease, non-cardiovascular disease, and all causes. We also defined three additional cardiovascular end points: fatal coronary heart disease, fatal stroke, and other fatal cardiovascular disease (such as non-coronary heart disease and non-stroke), based on diagnostic codes as defined in the SCORE project (systematic coronary risk evaluation project).[18] In the current study we split mortality from non-coronary atherosclerotic cardiovascular disease (non-coronary heart disease-cardiovascular disease) into mortality from stroke and other cardiovascular disease. An end point for fatal coronary heart disease was obtained from hospital records, which were systematically reviewed according to the monitoring of trends and determinants in cardiovascular disease (MONICA) protocol.[19]

For stroke mortality we used ICD-9 (ninth revision) codes 431, 433, 434, 436, and 438 and ICD-10 (10th revision) codes I61, I63, I64, I66, and I69.

At the start of the study, there were 18 903 participants, of whom 68 (0.36%) were lost to follow-up for cause specific mortality and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or body mass index (BMI) and were omitted. This left a sample of 18 725 (99%), with 470 990 years of follow-up during which 10 358 participants died. For cause specific mortality, 4323 died from cardiovascular disease and 6035 from non-cardiovascular disease. The 4323 deaths from cardiovascular disease consisted of 2810 deaths from coronary heart disease, 927 from stroke, and 586 from other forms of cardiovascular disease.

Statistical analysis

We used Cox proportional hazards to estimate the relative risk of death (hazard ratio) after adjusting for demographic and baseline risk factors for cardiovascular disease. Significance testing was two sided and based on a 5% probability level. Risk factors for mortality were entered into the Cox model in a stepwise manner, including those with P values under 0.2 for multivariable adjustment. For all cause mortality, we adjusted for age, BMI, education (primary, secondary, junior college, or university), smoking (none, current, previous), and systolic and diastolic blood pressure. For mortality from cardiovascular disease we additionally adjusted for current diabetes mellitus, cholesterol concentration, self reported history of coronary event, self reported current use of antihypertensive drugs, and use of oral contraceptives in women.

We tested the Cox models for possible violations of the proportional hazards assumption.[20 21] The assumption was not violated except for men with migraine without aura when death from coronary heart disease was the end point. When participants were censored after 30 years of follow-up, the proportional hazards assumption held. This resulted in somewhat lower hazard ratio for all three categories of headache compared with when the follow-up was up to 40 years. We also used a log–log plot. The curves for the groups in the current study were roughly parallel, indicating no violation of the proportionality of the hazards assumption.

We also estimated median life expectancy at age 50 by headache status from a Cox model adjusted for age. Men and women were compared descriptively with respect to headache/migraine status and mortality from cardiovascular disease through Nelson-Aalen cumulative hazard curves.[22 23] We estimated the absolute 10 year risk of mortality from all causes and cardiovascular disease by sex and headache status from the Cox model at ages 50, 60, and 70. The software package used was Stata version 9 (StataCorp LP, College Station, TX, USA) and SAS/STAT software version 9.2.

RESULTS

Table 1 shows the characteristics of the study participants. There were 9044 men and 9681 women, with an average age of 52.8 (range 33-81) at study entry. Overall, 11% (2023) of the participants (6% (571) of men, 15% (1452) of women) were classified as having migraine, including 3% with migraine without aura (1% (128) of men, 5% (498) of women) and 8% with migraine with aura (5% (443) of men, 10% (954) of women). Among participants with aura, the proportion with visual aura, sensory aura, and both visual and sensory aura was 72%, 17%, and 11% for men and 65%, 17%, and 19% for women, respectively. Within the migraine with aura group, 81% (358) of the men and 89% (849) of the women reported having at least one other migraine symptom.

Table 1 | Characteristics of men and women at first examination according to migraine and headache status in Reykjavik Study (n=18 725*). Figures are percentages of participants unless stated otherwise

	Men					Women				
Characteristic	No headache	Non-migraine headache†	Migraine	Migraine without aura‡	Migraine with aura§	No headache	Non-migraine headache†	Migraine	Migraine without aura‡	Migraine with aura§
Mean (SD) age (years)	52.7 (8.6)	51.5 (8.7)	50.6 (8.2)	49.9 (7.3)	50.8 (8.4)	54.4 (9.0)	52.1 (9.0)	50.7 (8.4)	49.9 (8.1)	51.1 (8.6)
Mean (SD) BMI	25.8 (3.4)	25.9 (3.5)	25.6 (3.3)	25.6 (3.2)	25.6 (3.3)	25.2 (4.2)	25.1 (4.4)	24.8 (4.2)	24.7 (4.0)	24.9 (4.3)
Mean (SD) cholesterol (mmol/l)	6.4 (1.1)	6.3 (1.0)	6.4 (1.1)	6.2 (1.1)	6.4 (1.1)	6.6 (1.3)	6.6 (1.2)	6.5 (1.2)	6.4 (1.2)	6.6 (1.2)
Mean (SD) systolic blood pressure (mm Hg)	141.1 (21.1)	139.9 (21.6)	137.9 (20.6)	139.3 (22.5)	137.5 (20.1)	136.8 (22.5)	135.7 (21.8)	133.7 (20.7)	132.3 (19.4)	134.5 (21.3)
Mean (SD) diastolic blood pressure (mm Hg)	89.3 (11.2)	90.2 (12.3)	88.8 (11.4)	90.6 (12.4)	88.3 (11.1)	84.1 (11.3)	84.3 (11.3)	84.1 (11.4)	83.3 (11.1)	84.5 (11.5)
Pulse pressure (mm Hg)	51.9 (15.0)	49.8 (14.2)	49.1 (13.8)	48.8 (13.8)	49.2 (13.8)	52.7 (16.1)	51.5 (15.5)	49.7 (14.5)	49.0 (13.1)	50.0 (15.2)
No of participants	7068	1405	571	128	443	6003	2226	1452	498	954
Headache	NA	100	100	100	100	NA	100	100	100	100
Pain, unilateral	NA	30	58	81	51	NA	27	67	80	60
Nausea/vomiting	NA	4	37	66	28	NA	9	62	80	53
Photophobia	NA	7	46	68	40	NA	7	59	65	56
Visual symptoms	NA	NA	64	NA	82	NA	NA	55	NA	84
Sensory symptoms	NA	NA	22	NA	28	NA	NA	23	NA	35
Elementary or less education	33	36	38	33	39	55	54	55	50	57
Hypertension treatment	7	8	8	9	8	11	12	10	8	11
Current smoking	55	56	56	52	58	41	40	40	36	42
Former smoking	23	24	24	25	23	15	15	16	18	16
Medical hormone use	0.3	0.4	1	1	1	5	7	9	8	9
Oral contraceptive use	NA	NA	NA	NA	NA	3	5	6	6	5
Diabetes	4	5	4	6	4	3	3	3	2	4
History of coronary event¶	3	2	1	0	1	1	0.4	0.4	0.4	0.4

NA=not applicable.
*Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI.
†Headache without or with one symptom of migraine once or more a month.
‡2-3 of unilateral, photophobia, nausea symptoms.
§Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.
¶Myocardial infarction, angioplasty, or coronary artery bypass graft.

Participants with migraine and headache were significantly younger than those without headache. Systolic blood pressure was lower among men with migraine than among men without headache (adjusted for age and use of antihypertensive drugs). Pulse pressure was lower among men and women with migraine than those without headache and lower among men with non-migraine headache than those without headache (table 1). Compared with those without headache, people with migraine or with migraine with aura had less education and were more likely to be taking antihypertensive drugs or hormone treatment, or both.

Migraine and non-migraine headache

Compared with people with no headache, those with migraine were at significantly increased risk of mortality from all causes (hazard ratio 1.15, 95% confidence interval 1.08 to 1.23, P<0.001, table 2) and from cardiovascular disease (1.22, 1.10 to 1.36, P<0.001, table 3). The risk was similar with and without adjustment for risk factors for cardiovascular disease. In models stratified by sex, men and women with migraine were at similarly increased risk of all cause mortality (P=0.87 for interaction by sex), but for mortality from cardiovascular disease men were at marginally higher risk than women (P=0.057 for interaction by sex). Women, but not men, with non-migraine headache were also at increased risk of mortality from cardiovascular disease. The above results were similar when we excluded the 266 people with a history of coronary artery disease from the model. Table 4 shows results for mortality from non-cardiovascular cause.

When we divided cardiovascular disease mortality into deaths from coronary heart disease, stroke, or other cardiovascular disease, people with migraine were at increased risk of death from coronary heart disease (sex and multivariable adjusted hazard ratio 1.22, 1.07 to 1.39, P=0.003, table 5) and stroke (1.30, 1.05 to 1.61, P=0.017, table 6). Risk of death from coronary heart disease and stroke, however, was significant only for men with migraine in the sex stratified models. Men and women with migraine were not at increased risk of mortality from other cardiovascular diseases (table 7).

Table 2 | Age and multivariable* adjusted hazard ratios (95% confidence intervals) for mortality from all cause according to migraine status in men and women in Reykjavik Study (n=18 725†)

	No headache	Non-migraine headache‡	Migraine	Migraine without aura§	Migraine with aura¶
Men					
Died/total	4519/7068	845/1405	364/571	73/128	291/443
Age adjusted	1.00	0.99 (0.92 to 1.07)	1.12 (1.01 to 1.25)**	0.92 (0.73 to 1.17)	1.19 (1.05 to 1.36)**
Multivariable adjusted	1.00	0.99 (0.92 to 1.06)	1.16 (1.04 to 1.29)**	0.95 (0.76 to 1.20)	1.23 (1.09 to 1.38)**
Women					
Died/total	2958/6003	1008/2226	664/1452	198/498	466/954
Age adjusted	1.00	1.02 (0.95 to 1.10)	1.12 (1.03 to 1.22)**	1.00 (0.86 to 1.15)	1.18 (1.07 to 1.31)**
Multivariable adjusted	1.00	1.04 (0.97 to 1.12)	1.16 (1.07 to 1.26)**	1.06 (0.92 to 1.22)	1.21 (1.09 to 1.33)**
Men and women					
Died/total	7477/13 071	1853/3631	1028/2023	271/626	757/1397
Age-sex adjusted	1.00	1.01 (0.96 to 1.06)	1.12 (1.05 to 1.19)**	0.97 (0.86 to 1.09)	1.18 (1.10 to 1.27)**
Multivariable adjusted	1.00	1.01 (0.96 to 1.07)	1.15 (1.08 to 1.23)**	1.02 (0.91 to 1.16)	1.21 (1.12 to 1.30)**

*Age, BMI, smoking (no, current, previous), education (primary, secondary, college/university), systolic and diastolic blood pressure, and use of antihypertensive drugs.
†Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI, leaving n=18 725 with 470 990 years of follow-up.
‡Headache without or with one symptom of migraine once or more a month.
§2-3 of unilateral, photophobia, nausea symptoms.
¶Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.
**Significant at P<0.05.

Migraine with aura and without aura

Among people with migraine, those with migraine with aura were at increased risk of mortality from all causes and cardiovascular disease (tables 2 and 3), but no increased risk was seen in those with migraine without aura. We studied the long term effects of migraine on mortality from cardiovascular disease using cumulative hazard curves. Men with migraine with aura were at marginally higher risk than women with migraine with aura (figure); this is also reflected in table 3, but this difference was marginally significant (P=0.053 for interaction by sex). Women with migraine with aura were still at marginally significantly increased risk of cardiovascular disease mortality compared with women with no headache (1.18, 1.00 to 1.40, P=0.053, table 3).

The increased risk of mortality from cardiovascular disease in people with migraine with aura was higher among men than women for coronary heart disease and stroke, although not significantly; hazard ratios were 1.43 in men versus 1.17 in women for mortality from coronary heart disease (table 5) and 1.76 in men versus 1.26 in women for mortality from stroke (table 6) (P=0.12 and 0.15 for interaction by sex for coronary heart disease and stroke mortality). To investigate this finding further, we divided non-cardiovascular disease

Table 3 | Age and multivariable* adjusted hazard ratios (95% confidence intervals) for mortality from cardiovascular disease according to migraine status in men and women in Reykjavik Study (n=18 725†)

	No headache	Non-migraine headache‡	Migraine	Migraine without aura§	Migraine with aura¶
Men					
Died/total	2086/7068	388/1405	189/571	38/128	151/443
Age adjusted	1.00	0.99 (0.89 to 1.10)	1.28 (1.11 to 1.49)**	1.07 (0.78 to 1.48)	1.35 (1.15 to 1.60)**
Multivariable adjusted	1.00	0.97 (0.87 to 1.08)	1.35 (1.17 to 1.57)**	1.14 (0.83 to 1.57)	1.42 (1.20 to 1.68)**
Women					
Died/total	1061/6003	377/2226	222/1452	66/498	156/954
Age adjusted	1.00	1.12 (1.00 to 1.26)	1.15 (0.99 to 1.33)	1.04 (0.81 to 1.34)	1.20 (1.01 to 1.42)**
Multivariable adjusted	1.00	1.13 (1.01 to 1.27)**	1.16 (1.00 to 1.34)	1.09 (0.85 to 1.40)	1.18 (1.00 to 1.40)
Men and women					
Died/total	3147/13 071	765/3631	411/2023	104/626	307/1397
Age-sex adjusted	1.00	1.04 (0.96 to 1.13)	1.19 (1.07 to 1.32)**	1.02 (0.84 to 1.24)	1.25 (1.11 to 1.41)**
Multivariable adjusted	1.00	1.04 (0.96 to 1.13)	1.22 (1.10 to 1.36)**	1.10 (0.91 to 1.34)	1.27 (1.13 to 1.43)**

*Age, BMI, smoking (no, current, previous), education (primary, secondary, college/university), systolic and diastolic blood pressure, use of antihypertensive drugs, cholesterol concentration, diabetes, history of coronary artery disease, and birth control use for women.
†Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI, leaving n=18 725 with 470 990 years of follow-up.
‡Headache without or with one symptom of migraine once or more a month.
§2-3 of unilateral, photophobia, nausea symptoms.
¶Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.
**Significant at P<0.05.

Table 4 | Age and multivariable* adjusted hazard ratios (95% confidence intervals) for mortality from non-cardiovascular disease (mortality from causes other than cardiovascular disease) according to migraine status in men and women in Reykjavik Study (n=18 725†)

	No headache	Non-migraine headache‡	Migraine	Migraine without aura§	Migraine with aura¶
Men					
Died/total	2433/7068	457/1405	175/571	35/128	140/443
Age adjusted	1.00	0.99 (0.90 to 1.09)	0.99 (0.85 to 1.15)	0.81 (0.58 to 1.13)	1.05 (0.88 to 1.24)
Multivariable adjusted	1.00	0.98 (0.89 to 1.09)	1.00 (0.86 to 1.17)	0.83 (0.59 to 1.16)	1.05 (0.89 to 1.25)
Women					
Died/total	1897/6003	631/2226	442/1452	132/498	310/954
Age adjusted	1.00	0.97 (0.88 to 1.06)	1.11 (1.00 to 1.23)	0.97 (0.81 to 1.16)	1.17 (1.04 to 1.32)**
Multivariable adjusted	1.00	0.99 (0.90 to 1.08)	1.14 (1.02 to 1.26)**	1.02 (0.86 to 1.22)	1.19 (1.06 to 1.35)**
Men and women					
Died/total	4330/13 071	1088/3631	617/2023	167/626	450/1397
Age-sex adjusted	1.00	0.98 (0.91 to 1.05)	1.07 (0.98 to 1.17)	0.93 (0.80 to 1.09)	1.13 (1.03 to 1.25)**
Multivariable adjusted	1.00	0.99 (0.92 to 1.05)	1.10 (1.01 to 1.19)**	0.97 (0.83 to 1.14)	1.15 (1.04 to 1.27)**

*Age, BMI, smoking (no, current, previous), education (primary, secondary, college/university), systolic and diastolic blood pressure, and use of antihypertensive drugs.
†Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI, leaving n=18 725 with 470 990 years of follow-up.
‡Headache without or with one symptom of migraine once or more a month.
§2-3 of unilateral, photophobia, nausea symptoms.
¶Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.
**Significant at P<0.05.

into cancer and non-cancer and found that the risk was increased only for mortality other than cancer 1.33, 1.13 to 1.57, P=0.001) (see appendix 2 on bmj.com).

Overall, using total mortality, our model suggests that at age 50 men and women with migraine with aura had a median loss of 1.5 and 1.4 years of life, respectively, compared with those without headache (see appendix 3 on bmj.com).

At age 50 the absolute risk of all cause mortality was low but still considerably higher for men than for women. For example, the 10 year risk for men aged 50 was 6.8% in those with no headache and 8.0% in those with migraine with aura; the corresponding values for women were 3.0% and 3.6%. At age 70 the absolute 10 year risk had risen to 40.6% and 46.1% for men and 24.1% and 27.9% for women (see appendix 4 on bmj.com).

DISCUSSION

Principal findings

In this cohort study with over 470 000 person years and a median follow-up of 26 years, men and women with migraine with aura were shown to be at increased risk of mortality from all causes and cardiovascular disease,

Table 5 | Risk of mortality from coronary heart disease according to migraine status in men and women in Reykjavik Study (n=18 725*). Figures are age and multivariable† adjusted hazard ratios (95% confidence intervals)

	No headache	Non-migraine headache‡	Migraine	Migraine without aura§	Migraine with aura¶
Men					
Died/total	1473/7068	275/1405	136/571	26/128	110/443
Age adjusted	1.00	0.99 (0.87 to 1.12)	1.29 (1.08 to 1.54)**	1.03 (0.70 to 1.52)	1.38 (1.13 to 1.67)**
Multivariable adjusted	1.00	0.96 (0.85 to 1.10)	1.36 (1.14 to 1.62)**	1.12 (0.76 to 1.65)	1.43 (1.18 to 1.74)**
Women					
Died/total	590/6003	213/2226	123/1452	35/498	88/954
Age adjusted	1.00	1.13 (0.96 to 1.32)	1.13 (0.93 to 1.37)	0.98 (0.69 to 1.38)	1.20 (0.96 to 1.51)
Multivariable adjusted	1.00	1.14 (0.98 to 1.34)	1.13 (0.93 to 1.37)	1.03 (0.73 to 1.46)	1.17 (0.93 to 1.47)
Men and women					
Died/total	2063/13 071	488/3631	259/2023	61/626	198/1397
Age-sex adjusted	1.00	1.04 (0.94 to 1.14)	1.19 (1.04 to 1.35)**	0.97 (0.75 to 1.25)	1.28 (1.10 to 1.48)**
Multivariable adjusted	1.00	1.03 (0.94 to 1.14)	1.22 (1.07 to 1.39)**	1.05 (0.82 to 1.37)	1.28 (1.11 to 1.49)**

*Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI, leaving n=18 725 with 470 990 years of follow-up.
†Age, BMI, smoking (no, current, previous), education (primary, secondary, college/university), systolic and diastolic blood pressure, and use of antihypertensive drugs.
‡Headache without or with one symptom of migraine once or more a month.
§2-3 of unilateral, photophobia, nausea symptoms.
¶Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.
**Significant at P<0.05.

Table 6 | Risk of mortality from stroke* according to migraine status in men and women in Reykjavik Study (n=18 725†). Figures are age and multivariable‡ adjusted hazard ratios (95% confidence intervals)

	No headache	Non-migraine headache§	Migraine	Migraine without aura¶	Migraine with aura**
Men					
Died/total	373/7068	63/1405	37/571	6/128	31/443
Age adjusted	1.00	0.92 (0.70 to 1.20)	1.46 (1.04 to 2.05)††	0.97 (0.43 to 2.18)	1.62 (1.12 to 2.34)††
Multivariable adjusted	1.00	0.90 (0.69 to 1.18)	1.55 (1.10 to 2.18)††	0.96 (0.43 to 2.15)	1.76 (1.22 to 2.54)††
Women					
Died/total	292/6003	99/2226	63/1452	18/498	45/954
Age adjusted	1.00	1.08 (0.86 to 1.36)	1.20 (0.91 to 1.58)	1.05 (0.65 to 1.69)	1.27 (0.92 to 1.74)
Multivariable adjusted	1.00	1.08 (0.86 to 1.36)	1.20 (0.91 to 1.59)	1.08 (0.67 to 1.75)	1.26 (0.92 to 1.73)
Men and women					
Died/total	665/13 071	162/3631	100/2023	24/626	76/1397
Age-sex adjusted	1.00	1.01 (0.85 to 1.20)	1.27 (1.03 to 1.58)††	1.01 (0.67 to 1.53)	1.38 (1.09 to 1.76)††
Multivariable adjusted	1.00	1.00 (0.84 to 1.19)	1.30 (1.05 to 1.61)††	1.06 (0.70 to 1.60)	1.40 (1.10 to 1.78)††

*ICD-9 codes 431, 433, 434, 436, 438 and ICD-10 codes I61, I63, I64, I66, and I69.
†Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI, leaving n=18 725 with 470 990 years of follow-up.
‡Age, BMI, smoking (no, current, previous), education (primary, secondary, college/university), systolic and diastolic blood pressure, and use of antihypertensive drugs.
§Headache without or with one symptom of migraine once or more a month.
¶2-3 of unilateral, photophobia, nausea symptoms.
**Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.
††Significant at P<0.05.

while those with migraine without aura were not at increased risk. Risk of mortality from cardiovascular disease was marginally more increased in men than in women with migraine and aura. Migraine with aura is an independent risk factor for cardiovascular and all cause mortality in men and women but weaker than major established risk factors, such as cigarette smoking, diabetes, and high blood pressure.

Strengths and limitations

This study had a large cohort, with a broad age range, long follow-up, and comprehensive data on conventional risk factors for cardiovascular disease at baseline as well as high ascertainment (>99%) of cause specific mortality. The cohort is population based, which adds to the generalisability of our results. Although our classification of migraine precedes the 2004 IHS criteria, the questions are similar to those currently asked in the IHS criteria and cover the most common symptoms of migraine.

We did not ask about symptoms of migraine in those who reported having headache less than once a month and so are therefore likely to capture only those with higher attack frequency. People who had migraine

Table 7 | Risk of mortality from cardiovascular disease other than coronary heart disease and stroke according to migraine status in men and women in Reykjavik Study (n=18 725*). Figures are age and multivariable† adjusted hazard ratios (95% confidence intervals)

	No headache	Non-migraine headache†	Migraine	Migraine without aura‡	Migraine with aura§
Men					
Died/total	240/7068	50/1405	16/571	6/128	10/443
Age adjusted	1.00	1.14 (0.84 to 1.54)	0.97 (0.58 to 1.60)	1.46 (0.65 to 3.29)	0.80 (0.43 to 1.51)
Multivariable adjusted	1.00	1.12 (0.83 to 1.53)	1.04 (0.63 to 1.73)	1.54 (0.68 to 3.47)	0.87 (0.46 to 1.64)
Women					
Died/total	179/6003	65/2226	36/1452	13/498	23/954
Age adjusted	1.00	1.19 (0.89 to 1.58)	1.16 (0.81 to 1.67)	1.29 (0.73 to 2.28)	1.10 (0.71 to 1.71)
Multivariable adjusted	1.00	1.21 (0.91 to 1.61)	1.20 (0.83 to 1.72)	1.33 (0.75 to 2.35)	1.13 (0.73 to 1.76)
Men and women					
Died/total	419/13 071	115/3631	52/2023	19/626	33/1397
Age sex adjusted	1.00	1.15 (0.93 to 1.42)	1.06 (0.79 to 1.42)	1.29 (0.81 to 2.05)	0.97 (0.68 to 1.38)
Multivariable adjusted	1.00	1.15 (0.93 to 1.42)	1.12 (0.83 to 1.50)	1.39 (0.87 to 2.21)	1.00 (0.70 to 1.43)

*Of original 18 903 participants, 68 (0.36%) were lost to follow-up and 110 (0.58%) had missing data on blood pressure, cholesterol concentration, or BMI., leaving n=18 725 with 470 990 years of follow-up.
†Age, BMI, smoking (no, current, previous), education (primary, secondary, college/university), systolic and diastolic blood pressure, and use of antihypertensive drugs.
‡Headache without or with one symptom of migraine once or more a month.
§2-3 of unilateral, photophobia, nausea symptoms.
¶Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.

aura exclusively, without headache, would be included in the "no headache" group because of our screening question. We cannot draw any conclusions from the current study about the risk of mortality for people with migraine with low frequency of attacks (less than once a month) and those with migraine aura without headache.

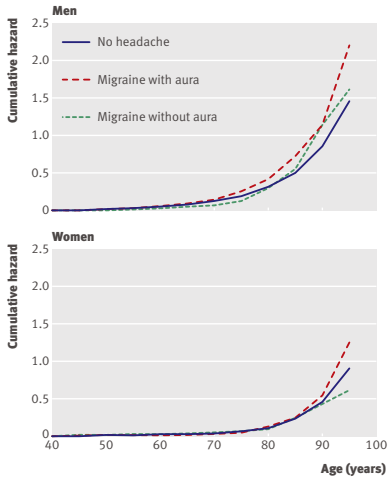
The risk of cardiovascular outcomes might be higher in people with more frequent attacks of migraine. Kurth et al looked at frequency of attacks and risk of cardiovascular disease in a cohort of US women.[24] They reported a J-shaped association between attack frequency and risk. If this J-shaped association applies to our current study, our estimates might be somewhat lower than we would have found if we had included everyone with migraine, although this is speculative.

The prevalence of aura (as a proportion of the total migraine population) is higher than has been reported in other population studies and might include commonly occurring non-specific visual symptoms such as blurring. The result of this misclassification would probably attenuate the relation between migraine with aura and mortality. We note that our prevalence of migraine overall (with and without aura combined), however, is highly consistent with previous studies.[25]

Finally, the combination of visual symptoms and headache can be symptoms of a transient ischaemic attack. If this were misclassified as migraine with aura in our study, it might exaggerate the association between migraine and mortality from cardiovascular disease. Our diagnosis of migraine, however, required headache at least once a month in the past 12 months, which is not a feature of transient ischaemic attack. Therefore we believe it is unlikely that this type of misclassification would have appreciably affected our results.

As we have data on vascular risk factors only at baseline, we did not adjust for potential changes in such risk factors that might have developed after the start of the study. These risk factors in adults tend to track over time[26]—that is, those at high risk tend to stay at high risk during follow-up and those at low risk tend to stay at low risk. While residual confounding because of imperfect control for vascular risk factors at baseline or after the start of the study is a possibility, we note that the hazard ratios scarcely changed after adjustment, arguing against a strong role for this sort of error.

Although about only 2% of affected people have new onset migraine over the age of 50,[27] the younger people in the cohort might have developed migraine after the study started and not been counted. We suggest that such a low percentage of people with migraine would be unlikely to change the risk estimates in the current study. Neither data on migraine specific treatment, such as ergotamine and triptans, nor data on the use of analgesics or steroid treatment were available. We could not therefore estimate the potential modifying effects of these drugs on the association between migraine and cardiovascular disease.



Migraine status and Nelson-Aalen cumulative hazards for mortality from cardiovascular disease. For men and women curve for non-migraine headache overlays curve for no headache and was therefore omitted

Comparison with other studies

This population based cohort study measured mortality from all causes and cardiovascular disease in men and women with migraine separately by aura status. Our findings are consistent with the increasing evidence that migraine, particularly migraine with aura, is associated with cardiovascular disease.[1 3 4 28] Previous reports in which migraine has been shown to be protective for all cause mortality[11 12 14] could be explained by methodological differences with this study. For example, two of these studies[12 14] were based on patient based rather than population based samples. Furthermore, one of these studies[14] identified those with migraine based in part on their use of triptans, which are contraindicated in people with risk factors for cardiovascular disease. The aim of the two studies[12 14] was not to compare risk in those with and without migraine but to assess possible risk of triptans in people with migraine. The fact that those two studies showed a protective effect could also explain why a recent meta-analysis of five studies (including those two studies) showed no risk for mortality from cardiovascular disease associated with migraine overall (with and without aura combined) (relative risk 1.03, 0.79 to 1.34).[6] Only one study included in that meta-analysis estimated the risk of mortality separately in people with migraine with aura.[4] This study suggested that women with migraine with aura were at about twice the risk of cardiovascular mortality compared with women without headache.

The hazard ratios for mortality for cardiovascular disease in men with migraine were somewhat higher than the corresponding values for all cause mortality.

WHAT IS ALREADY KNOWN ON THE TOPIC

Individuals with migraine with aura (but not without aura) are at almost twice the risk of ischaemic stroke than other people

Individuals with migraine (with and without aura combined) are not at increased risk of death from cardiovascular disease

Compared with women without headache, women with migraine with aura (but not without aura) are at increased risk of death from cardiovascular disease after age 45

WHAT THIS STUDY ADDS

Migraine with aura is an independent risk factor for cardiovascular and all cause mortality in both men and women but is weaker than major established risk factors, such as smoking, diabetes, and high blood pressure

Women with migraine with aura were at increased risk of mortality from non-cardiovascular disease

People with migraine, particularly those with aura, were at increased risk of death from coronary heart disease and stroke

The risk was independent of traditional risk factors for cardiovascular disease measured at baseline. Several studies have reported greater risk of stroke in people with migraine[1 6 28] than in others, especially for those with aura.[1 4 6 28] The risk of coronary heart disease among people with migraine varies more between studies, from being lower than normal to being moderately increased.[6] In our study the risk increase for mortality from coronary heart disease was mainly confined to men with migraine with aura.

The increased risk of overall mortality or mortality related to cardiovascular disease associated with migraine with aura is significant but modest: 20% for women and 20% for men, with respect to all cause mortality, and 18% for women and 42% for men, with respect to cardiovascular disease mortality.

We estimated that at age 50 men and women with migraine with aura had a median loss of 1.5 or 1.4 years of life compared with those without headache. By way of comparison with more established risk factors for all cause mortality, the median loss of life in the Reykjavik Study for those with untreated high blood pressure (≥160 mm Hg), type 2 diabetes, and smoking 15 cigarettes or more a day was, respectively, about 5, 5, and 13 years for men and 3, 3, and 9 years for women[29 30] (see appendix 3 on bmj.com).

In people with migraine with aura, compared with those without headache, the excess absolute 10 year risk of all cause mortality at age 50 was low: 1.2% for men (8.0% *v* 6.8% risk of all cause mortality) and 0.6% for women (3.6% *v* 3.0%). At age 70, the excess absolute risk of all cause mortality in people with migraine with aura was higher, at 5.5% for men (46.1% *v* 40.6%) and 3.8% for women (27.9% *v* 24.1%).

Potential mechanisms

Several mechanisms could explain the link between migraine and cardiovascular disease, though none has been definitively established. Migraine and ischaemic events have been linked through a genetic component.[31] They might reflect associations between migraine with aura and vasculopathy[32] and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS).[33] Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme in the metabolism of homocysteine, derived from the amino acid methionine, and a risk factor for cerebral small vessel disease[34] and migraine.[35] Migraine could directly cause an ischaemic event that is from a migrainous infarct, but such events are rare, about 3% of all strokes,[36] and can therefore account for only a small proportion of all strokes in people with migraine. There is increasing evidence that migraine is associated with coronary heart disease,[4 37] and one study reported an association between migraine and an increased prevalence of conventional vascular risk factors.[9] The current data show little difference in risk factors between those with and without migraine, which is in line with previous studies on people with migraine in the Reykjavik Study.[7 8] Our results were similar with and without adjustment for conventional risk factors for cardiovascular disease, suggesting that the mechanism(s) linking migraine to cardiovascular disease are from a different pathway. Others have reported that people with migraine, even in the absence of conventional risk factors, are at increased risk of stroke[37] and have decreased cerebral and peripheral vascular resistance, retinal microvascular signs, hypercoagulability, and inflammation,[31 38] supporting the hypothesis that migraine might be a systemic disorder that is affecting vasculature.[39] People with migraine have been shown to have altered vascular reactivity at a young age (under 25 years),[40] which indicates that there might be a factor affecting both the onset of migraine and progression of cardiovascular disease early in life. A recent study reported that people with migraine without aura had reduced function and number of endothelial progenitor cells,[38] which has been associated with higher Framingham risk scores in people with coronary heart disease[41] and increased risk of mortality from cardiovascular disease.[42]

Implications

People with migraine, particularly those with migraine with aura, are at a modestly increased risk of mortality, independent of classic risk factors for cardiovascular disease measured in mid-life. The absolute risk is low, and the focus should be on conventional risk factors, such as hypertension, smoking, and adverse lipid profile, for reducing the risk of cardiovascular disease, regardless of migraine status.

Future research

More research is needed on the association between migraine and mortality from cardiovascular disease, non-cardiovascular disease, and all causes, including studies to identify whether there are specific subgroups of people with migraine who are at particular risk because of genetic or environmental factors. Future studies should assess aura status and frequency of attacks in detail, and prospective studies can monitor changes in the risk profile for cardiovascular disease

over time to better understand the aetiology and pathophysiology of migraine in its development. Finally, studies are needed to determine if reducing the frequency of attacks with migraine preventive treatment might reduce the risk of cardiovascular disease.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no company has supported the submitted work; LSG has received a travel grant from the Pharmaceutical Society of Iceland Science Fund, AIS has served on advisory boards for Endo Pharmaceuticals and OrthoMcNeil Neurologics, has received an honorarium and a travel grant from the National Headache Foundation and a travel grant from the American Headache Society; no other relationships or activities that could appear to have influenced the submitted work.
Ethical approval: This study was approved by the Surgeon General's ethics committee 1969, and informed consent was given by all participants.
Data sharing: No additional data are available.

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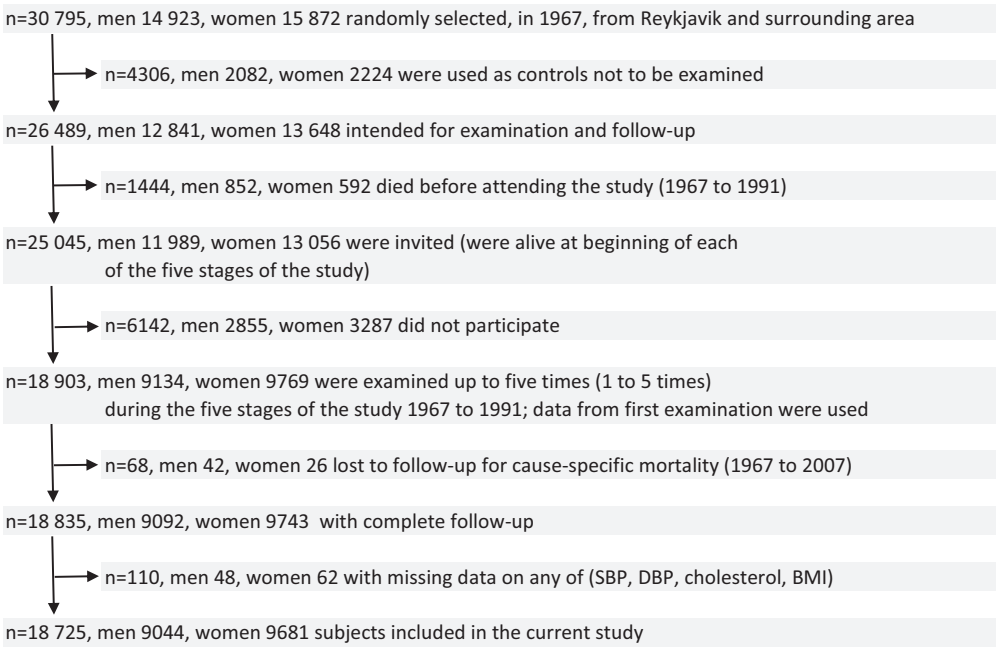
Appendix 1 Flow chart of participation and follow-up in the Reykjavik Study [posted as supplied by author]



Appendix 2 non-CV mortality split up in cancer mortality and mortality other than CV or cancer according to migraine status in men and women in the Reykjavik Study (n=18 725)* [posted as supplied by author]

	Hazard Ratio and (95% Confidence Interval)				
	No headache	Non-migraine headache□	Migraine	Migraine without aura□	Migraine with aura□
Cancer mortality					
Men					
Died/total	1333/7068	238/1405	93/571	16/128	77/443
age-adjusted	1.00	0.93 (0.81 to 1.07)	0.94 (0.76 to 1.16)	0.66 (0.40 to 1.07)	1.03 (0.82 to 1.29)
mv-adj.ll	1.00	0.92 (0.80 to 1.06)	0.94 (0.76 to 1.16)	0.68 (0.41 to 1.11)	1.03 (0.82 to 1.29)
Women					
Died/total	930/6003	306/2226	214/1452	68/498	146/954
age-adjusted	1.00	0.92 (0.80 to 1.04)	1.01 (0.87 to 1.18)	0.93 (0.73 to 1.20)	1.06 (0.89 to 1.26)
mv-adj.ll	1.00	0.93 (0.82 to 1.06)	1.04 (0.90 to 1.21)	0.99 (0.77 to 1.26)	1.07 (0.90 to 1.28)
Men and women					
Died/total	2363/13071	544/3631	307/2023	84/626	223/1397
age- & sex-adjusted	1.00	0.93 (0.84 to 1.02)	1.00 (0.88 to 1.13)	0.88 (0.70 to 1.09)	1.05 (0.92 to 1.21)
mv-adj.ll	1.00	0.93 (0.85 to 1.03)	1.02 (0.90 to 1.15)	0.92 (0.74 to 1.14)	1.06 (0.93 to 1.22)
Mortality other than CV or cancer					
Men					
Died/total	1100/7068	219/1405	82/571	19/128	63/443
age-adjusted	1.00	1.07 (0.92 to 1.23)	1.05 (0.84 to 1.32)	1.00 (0.63 to 1.57)	1.07 (0.83 to 1.38)
mv-adj.ll	1.00	1.06 (0.92 to 1.23)	1.07 (0.86 to 1.34)	1.02 (0.65 to 1.61)	1.08 (0.84 to 1.40)
Women					
Died/total	967/6003	325/2226	228/1452	64/498	164/954
age-adjusted	1.00	1.03 (0.90 to 1.16)	**1.21 (1.04 to 1.40)**	1.02 (0.79 to 1.31)	**1.30 (1.10 to 1.54)**
mv-adj.ll	1.00	1.05 (0.92 to 1.19)	**1.24 (1.07 to 1.44)**	1.07 (0.83 to 1.37)	**1.33 (1.13 to 1.57)**
Men and women					
Died/total	2067/13071	544/3631	310/2023	83/626	227/1397
age- & sex-adjusted	1.00	1.04 (0.94 to 1.14)	**1.15 (1.02 to 1.30)**	1.00 (0.80 to 1.25)	**1.22 (1.07 to 1.41)**
mv-adj.ll	1.00	1.05 (0.95 to 1.15)	**1.19 (1.05 to 1.34)**	1.04 (0.84 to 1.30)	**1.25 (1.09 to 1.43)**

* Subjects were originally 18 903, but 68 (0.36%) were lost to follow-up for cause specific mortality and 110 (0.58%) had missing data on blood pressure, cholesterol or body mass index, n=18 725 and in all 470 990 years of follow-up.

□ headache without or with one migrainous symptom once or more per month.

□ 2-3 of unilateral, photophobia, nausea symptoms.

§ Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.

ll multivariable-adjusted: age, body mass index, smoking (no, current, previous), education (primary, secondary, college-university), systolic and diastolic blood pressure and antihypertensive medical use.

Bolded values are statistically significant ($p<0.05$).

CV: Cardiovascular.

Appendix 3 Risk factors for mortality and loss of median life-time in years at age 50 [posted as supplied by author]

		All-cause mortality HR [95% CI]	Loss of median life-time in years
Men			
	smoking >=15 cig. /day*	**3.1 (2.5 to 3.8)**	13
	smoking <15 cig. /day*	**2.4 (1.9 to 3.1)**	9
	T2DM□	**1.6 (1.4 to 1.9)**	5
	SBP>=160 vs. SBP<130□	**1.5 (1.4 to 1.7)**	5
	Non-migraine headache□	1.0 (0.9 to 1.1)	0.3
	Migraine	1.1 (1.0 to 1.2)	1.0
	Migraine without aura ll	0.9 (0.7 to 1.1)	-1.2
	Migraine with aura□	**1.2 (1.0 to 1.3)**	1.5
Women			
	smoking >=15 cig. /day*	**3.7 (3.0 to 4.4)**	9
	smoking <15 cig. /day*	**2.3 (1.9 to 2.8)**	6
	T2DM□	**1.6 (1.4 to 1.9)**	3
	SBP>=160 vs. SBP<130□	**1.5 (1.4 to 1.6)**	3
	Non-migraine headache□	1.0 (0.9 to 1.1)	-0.1
	Migraine	1.1 (1.0 to 1.2)	0.9
	Migraine without aura ll	1.0 (0.8 to 1.1)	-0.4
	Migraine with aura□	**1.2 (1.1 to 1.3)**	1.4

Values are age adjusted unless otherwise indicated.

* cig.: cigarettes, estimates of HR and median life-time for smoking: 2930 men and 3084 women, age 34-61 years, from the Reykjavik Study with a median follow-up of 26 years.[37]

□ T2DM: type two diabetes mellitus, estimates of HR and median life-time for type two diabetes: combined values from the Reykjavik Study and Reykjavik AGES Study. Follow-up in the Reykjavik Study was 20 years and 3.5 years in Reykjavik AGES Study.[36]

□ Subjects on antihypertensive medication omitted, adjusted for smoking status.

§ Headache without or with one migrainous symptom twelve times or more per year.

ll 2-3 of unilateral, photophobia, nausea symptoms.

¶ Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.

Bolded values are statistically significant ($p<0.05$)

Appendix 4 Age adjusted absolute 10-year risk of CV and all-cause mortality according to migraine status [posted as supplied by author]

Endpoint	Absolute 10-year risk (%) and (95% Confidence Interval)				
Gender Adjustment	**No headache**	**Non-migraine headache**	**Migraine**	**Migraine without aura**	**Migraine with aura§**
All-cause					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Age 50	6.8 (6.3 to 7.3)	6.7 (6.1 to 7.3)	7.6 (6.7 to 8.5)	6.3 (4.8 to 7.7)	8.0 (7.0 to 9.0)
Age 60	17.4 (16.4 to 18.4)	17.3 (15.9 to 18.6)	19.4 (17.3 to 21.4)	16.2 (12.6 to 19.7)	20.3 (18.0 to 22.6)
Age 70	40.6 (38.4 to 42.7)	40.3 (37.4 to 43.2)	44.3 (40.1 to 48.2)	38.2 (30.6 to 45.0)	46.1 (41.5 to 50.4)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Age 50	3.0 (2.8 to 3.3)	3.1 (2.8 to 3.4)	3.4 (3.0 to 3.8)	3.0 (2.5 to 3.5)	3.6 (3.2 to 4.0)
Age 60	8.8 (8.1 to 9.5)	9.0 (8.2 to 9.8)	9.8 (8.8 to 10.8)	8.8 (7.4 to 10.1)	10.3 (9.2 to 11.5)
Age 70	24.1 (22.4 to 25.9)	24.6 (22.5 to 26.7)	26.7 (24.1 to 29.1)	24.0 (20.6 to 27.4)	27.9 (25.0 to 30.7)
CV mortality					
Men	(n=7068)	(n=1405)	(n=571)	(n=128)	(n=443)
Age 50	3.3 (3.0 to 3.6)	3.3 (2.8 to 3.7)	4.2 (3.5 to 4.9)	3.5 (2.4 to 4.7)	4.4 (3.6 to 5.2)
Age 60	9.3 (8.6 to 10.1)	9.3 (8.2 to 10.4)	11.8 (10.0 to 13.6)	10.0 (6.8 to 13.0)	12.4 (10.3 to 14.4)
Age 70	24.9 (22.8 to 27.0)	24.8 (21.8 to 27.6)	30.8 (26.3 to 35.1)	26.5 (18.5 to 33.6)	32.2 (27.1 to 36.8)
Women	(n=6003)	(n=2226)	(n=1452)	(n=498)	(n=954)
Age 50	0.6 (0.5 to 0.7)	0.6 (0.5 to 0.8)	0.7 (0.5 to 0.8)	0.6 (0.4 to 0.8)	0.7 (0.5 to 0.8)
Age 60	2.4 (2.1 to 2.8)	2.7 (2.3 to 3.1)	2.8 (2.3 to 3.3)	2.5 (1.8 to 3.2)	2.9 (2.3 to 3.5)
Age 70	9.9 (8.6 to 11.3)	11.1 (9.3 to 12.8)	11.4 (9.3 to 13.4)	10.3 (7.6 to 13.0)	11.8 (9.5 to 14.1)

 Headache without or with one migraineous symptom once or more per month.

 2-3 of unilateral, photophobia, nausea symptoms.

§ Migraine with visual or sensory symptoms, or both. Participants with symptoms of migraine without aura and migraine with aura were classified as migraine with aura.

CV: Cardiovascular.