

ORIGINAL RESEARCH ARTICLE

Marital status and risk of cardiovascular diseases: a systematic review and meta-analysis

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ABSTRACT

Background The influence of marital status on the incidence of cardiovascular disease (CVD) and prognosis after CVD is inconclusive. We systematically reviewed the literature to determine how marital status influences CVD and prognosis after CVD.

Methods A search of MEDLINE and Embase in January 2018 without language restriction was performed to identify studies that evaluated the association between marital status and risk of CVD. Search terms related to both marital status and CVD were used and included studies had to be prospective in design. The outcomes of interest were CVD, coronary heart disease (CHD) or stroke incidence and mortality. We performed random effects meta-analysis stratified by the types of population by calculating odds ratios (OR) and 95% confidence intervals (95% CI).

Results Our analysis included 34 studies with more than two million participants. Compared with married participants, being unmarried (never married, divorced or widowed) was associated with increased odds of CVD (OR 1.42; 95% CI 1.00 to 2.01), CHD (OR 1.16, 95% CI 1.04 to 1.28), CHD death (OR 1.43, 95% CI 1.28 to 1.60) and stroke death (OR 1.55, 95% CI 1.16 to 2.08). Being divorced was associated with increased odds of CHD ($P < 0.001$) for both men and women while widowers were more likely to develop a stroke ($P < 0.001$). Single men and women with myocardial infarction had increased mortality (OR 1.42, 95% CI 1.14 to 1.76) compared with married participants.

Conclusions Marital status appears to influence CVD and prognosis after CVD. These findings may suggest that marital status should be considered in the risk assessment for CVD and outcomes of CVD based on marital status merits further investigation.

INTRODUCTION

Cardiovascular disease (CVD) is associated with significant morbidity and mortality.¹ In order to reduce the burden of CVD, there is great interest in identifying risk factors in the general population so that those deemed to be at high risk for future cardiovascular events can be targeted for intervention. While 80% of the risk for future CVD can be predicted from known cardiovascular risk factors such as old age, male sex, hypertension, hyperlipidaemia, smoking and diabetes mellitus, the determinants for the remaining 20% risk remain unclear.²

One factor which may be associated with CVD is marital status and studies have reported

inconsistent findings. The benefits of marriage on health and mortality have been demonstrated for both sexes, in different ethnic groups and appear to be independent of various sociodemographic characteristics.^{3–4} Better prognosis in married individuals has been reported both after myocardial infarction^{3–10} and stroke,^{11–12} whereas, other studies found no influence of marital status on risk of future CVD.^{13–15} In addition, sex differences have been observed where the degree of ‘protection’ conferred in men from being married tends to be greater.^{16–17} The interpretation of marital status and CVD becomes more complex with the addition of divorced and widowed groups.^{15–18–20}

In view of these disparate findings reported in the literature, we conducted a systematic review and meta-analysis to evaluate the risk of CVD based on marital status and the influence of marital status on prognosis after CVD.

METHODS

This systematic review and meta-analysis was conducted and reported according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).²¹

Eligibility criteria

We selected studies which evaluated cardiovascular events or mortality in participants according to marital status. The included studies had at least two groups (married and unmarried, divorced or widowed) and followed participants for incident cardiovascular events or mortality outcome after incident CVD. Studies of patients with suspected coronary heart disease were also included but not pooled with other studies with myocardial infarction. Only prospective studies published since 2000 were retained for analysis to limit issues related to quality of study reporting and generalisability to contemporary clinical practice. There was no exclusion of studies based on the length of follow-up, language of publication or definition of cardiovascular events such as ischaemic heart disease, coronary heart disease, myocardial infarction and stroke. However, we excluded studies of heart failure, retrospective analyses, case-control studies and those studies which did not report the numerical association between marital status and outcome. Reviews were examined for additional studies that met the inclusion criteria.



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Search strategy

We searched MEDLINE and Embase from 2000 onwards using OVID SP with no date or language restriction. This search was last updated in January 2018. The exact free search terms were ('marital status' or 'married' or 'unmarried' or 'widowed' or 'divorced') AND ('myocardial infarction' or 'acute coronary syndrome' or 'coronary heart disease' or 'ischaemic heart disease' or 'ischaemic heart disease' or 'heart attack' or 'stroke' or 'cerebrovascular disease' or 'cerebrovascular accident'). We checked the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

Study selection process and data collection process

Two reviewers (CWW and CSK) independently screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The full articles of studies that potentially met the inclusion criteria were reviewed and the final decision to include or exclude was made with the other reviewers. Independent double extractions were performed by two reviewers (CWW and CSK) collecting data on study design, year, country, number of participants, mean age, % male, participant inclusion criteria, comparison groups and results, while independent double extractions for quality assessment table were completed by CWW and another reviewer (AN).

Risk of bias assessment

Quality assessment of the studies was conducted based on the recommendations of the Cochrane Handbook for Systematic Review and previous published systematic reviews of observational studies.²²

Data analysis

We used Review Manager V.5.3.5 (Nordic Cochrane Centre) to conduct random effects meta-analysis stratified by the type of population which were either general population, post stroke or post myocardial infarction and marital status. We used random effects because the studies were conducted in a wide range of settings in different populations, hence the need to take heterogeneity into account for the pooled effect estimate. Where possible, we chose to pool reported adjusted risk estimates from primary studies and when these data were not available, raw data were used to calculate unadjusted risk estimates. We used the I^2 statistic to assess statistical heterogeneity. I^2 values of 30–60% represent moderate levels of heterogeneity and sensitivity analysis was performed to evaluate analyses with high statistical heterogeneity. Publication bias was assessed by asymmetry testing with funnel plots if there was no evidence of significant heterogeneity.²³ Further subgroup analyses were performed to investigate the impact of sex differences combined with marital status on various cardiovascular outcomes. Further analyses were also performed with the exclusion of studies with unclear marital status ascertainment and another with the exclusion of studies with only crude results or unadjusted results available.

RESULTS

Description of studies included in analysis

The process of study selection is shown in figure 1. After screening, 32 studies were retained for inclusion and two additional studies were identified from a review yielding a total of 34 studies for analysis. Table 1 summarises the study designs and participant characteristics. These 34 studies, which took place in various countries including Russia, Denmark, Spain, USA, Sweden, UK, Canada, Israel, Gulf States, Japan, Finland,

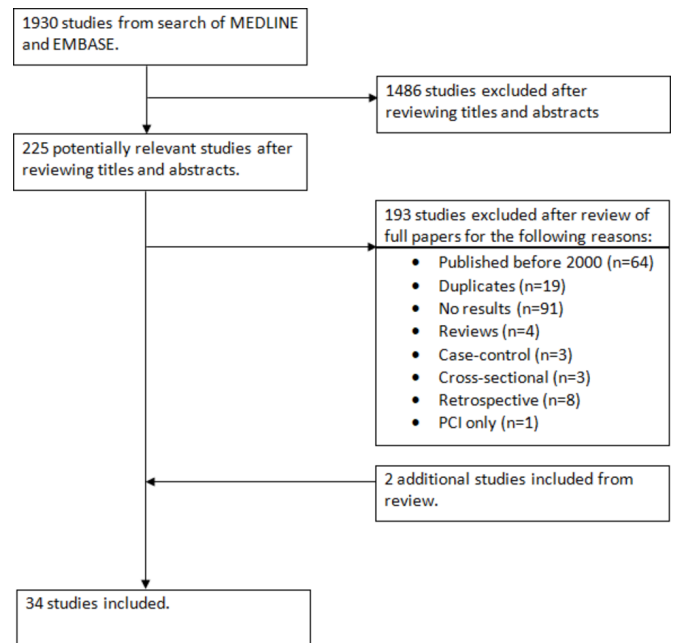


Figure 1 Flow diagram of study selection.

Greece, Turkey, Norway and China between 1963 and 2015. The follow-up period from these studies ranged from 30 days to 34 years. There were more than 2 million participants (ranging from 135 to 734 626 participants). Data on age are available for 1 137 571 participants from 25 studies with a mean of 58.4 years (range 42 to 77 years). The definition of unmarried used in each study is presented in the online supplementary table 1.

Quality assessment of included studies

The quality assessment of included studies is summarised in online supplementary table 2. Twenty-four studies were found to have used reliable methods for ascertaining the marital status which involved utilising databases,^{7 11 14–16 20 24 25} questionnaires,^{2 9 13 17 18 26–29} and interviews.^{9 12 19 25 30–34} Reliable outcome ascertainment was found in 25 studies either from databases,^{6 7 11 13–18 20 24 25 28–30 32 33 35–37} medical records,^{6 7 13 16 17 30 31 34} or assessment by healthcare professionals or research teams.^{2 18 19 29} Seventeen studies reported a low rate of loss to follow-up of <10%.^{2 6 7 9 13–15 17–20 24 29 30 32 33 35} Twenty-nine studies included adjusted analyses,^{3 6–10 13–20 24–27 29 31 33–38} three studies included unadjusted analysis^{9 11 12} and five studies had only crude results available.^{2 30 32 39 40} For assessment of publication bias, the funnel plots conducted showed no significant asymmetry in the pattern of distribution of studies (online supplementary figures 1–14).

Pooled analysis of marital status and cardiovascular outcomes

Mortality in the general population

The results for the general population as well as by gender are summarised in tables 2–4 (and online supplementary table 2 and online supplementary figures 1–2 and 4–13). Compared with married participants, unmarried participants were more likely to die from both CHD (OR 1.43, 95% CI 1.28 to 1.60, $I^2=57%$, $P<0.001$, $n=5$) and stroke (OR 1.55, 95% CI 1.16 to 2.08, $I^2=0%$, $P=0.003$, $n=2$) (figure 2A and figure 2B).

Being divorced was associated with an increased odds of CHD mortality (OR 1.33, 95% CI 1.04 to 1.70, $I^2=0%$, $n=3$) (online

Table 1 Study design and participant characteristics

Study ID	Study design; country; design	Total participants	Mean age	% male	Inclusion criteria
Akimova 2014 ²⁵	Prospective cohort study; Russia; 1996–2008	1609	–	49.4	Participants were Tyumen citizens aged 25–64 years
Andersen 2011 ¹¹	Prospective cohort study; Denmark; 2000–2007	26 818	71.2	51.5	Participants were patients with first-ever ischaemic stroke admission aged 18 and above in the Danish National Indicator Project
Bell 2013 ²⁶	Post-hoc analysis of trial and cohort study; USA; 1993–2010	3173	Mean age at stroke was 72.6	0	Participants were post-menopausal women aged 50–79, who were stroke-free at baseline with incident stroke before 2005 in the Women's Health Initiative trial
Consuegra-Sanchez 2015 ⁶	Prospective cohort study; Spain; 1998–2013	7408	66.1	73.3	Participants were patients with acute MI aged 18 and above who were admitted to the coronary care units of two hospitals in the Murcia region within 24 hours
Dupre 2015 ¹⁹	Prospective cohort study; USA; 1992–2010	15 827	54.3	45.9	Participants were ever married adults aged 45–80 years in the Health and Retirement Study
Dupre 2013 ³⁰	Prospective cohort study; USA; 1992–2010	2197	69.5	55.1	Participants had MI during the follow-up period in the Health and Retirement Study
Eaker 2007 ²⁷	Prospective cohort study; USA; 1971–1987	3682	48.5	48.1	Participants were in the Framingham Offspring Study, consisting of the offspring (and their spouses) of the Framingham Heart Study Original Cohort, enrolled in 1971 to 1974
Engstrom 2000 ¹⁴	Prospective cohort study; Sweden; 1977–1994	9351	48.5	0	Participants were women aged 28–55 years who attended the health examination programme at the Department of Preventive Medicine in Malmo
Engstrom 2004 ²⁸	Prospective cohort study; Sweden; 1990–2000	118 134	60	44.8	Participants were individuals aged between 40–89 years in Malmo, Sweden
Engstrom 2006 ²⁰	Prospective cohort study; Sweden; 1974–1997	6075	46.8	100	Participants were men without history of MI, stroke or cancer aged 28–61 years in Malmo, Sweden
Floud 2014 ¹³	Prospective study; UK; 1996–2011	7 346 26	59.7	0	Participants were women without history of heart disease or stroke in the Million Women Study
Gerward 2010 ⁷	Prospective cohort study; Sweden; 1974–2004	3542	–	85.7	Participants were individuals aged 27–61 years without history of MI in the Malmo Preventive Project
Ghosh-Swaby 2016 ²⁸	Prospective cohort study; Canada; published in 2016	2100	–	–	Participants had PCI after MI in the Canadian Observational Antiplatelet Study
Golbourt 2010 ²⁵	Prospective cohort study; Israel; 1963–1997	10 059	49.2	100	Participants were male civil servants and municipal employees in the Israeli Ischaemic Heart Disease study
Hadi 2012 ⁸	Prospective cohort study; Gulf States; 2008–2009	5334	56.8	79.0	Participants were post-ACS patients in the second Gulf Registry of Acute Coronary Events
Ikeda 2009 ¹⁷	Prospective cohort study; Japan; 1990–2004	90 987	51.9	47.7	Participants were Japan residents aged 40–69 years in the first and second cohort of the Japan Public Health Centre-based Prospective Study
Janzon 2004 ²⁴	Prospective cohort study; Sweden; 1977–1998	10 621	49.6	0	Participants were women without history of MI or stroke aged between 28–58 in Malmo, Sweden
Jayaram 2013 ³⁹	Prospective cohort study; US; 2003–2008	4853	50 to 80	66.7	Participants were post-acute MI patients aged 50 to 80 years from 31 USA sites.
Kilpi 2015 ¹⁶	Prospective cohort study; Finland; 1987–2007	2 992 81	–	49.4	Participants were individuals aged above 15 years in Finland
Kriegbaum 2008 ¹⁵	Prospective cohort study; Denmark; 1980–2005	8865	28 to 39	100	Participants were men born in Copenhagen in 1953 and living in Denmark in 1968
Malyutina 2004 ¹⁸	Prospective cohort study; Russia; 1984–1998	11 404	25 to 64	56.9	Participants were residents in Novosibirsk aged 25–64 years in the WHO MONICA Project
Maselko 2009 ³¹	Prospective cohort study; USA; 1992–2006	22 818	63.9	56	Participants were individuals born between 1900–1947 aged 50 years or above without history of stroke in the Health and Retirement Study
Matthews 2002 ²⁹	Post-hoc analysis of clinical trial; USA; published in 2002	10 904	46.4	100	Participants were men without definite evidence of clinical CHD but with above-average risk for death due to CHD because of high blood pressure, elevated serum cholesterol levels, and/or cigarette smoking in the Multiple Risk Factor Intervention Trial
Orth-Gomer 2000 ³²	Prospective cohort study; Sweden; 1991–1997	292	55.8	0	Participants were female acute MI or unstable angina patients aged 30–65 years in the Stockholm Female Coronary Risk Study
Panagiotakos 2008 ³	Prospective cohort study; Greece; 2003–2004	2090	66.7	75.9	Participants were patients hospitalised with ACS in the GREECS study
Quinones 2014 ³³	Prospective cohort study; Germany; 2000–2010	3766	28 to 74	75.4	Participants were patients with first episode of MI in Germany who survived longer than 28 days in the MONICA/KORA-myocardial infarction registry
Samanci 2004 ¹²	Prospective cohort study; Turkey; 1995–2001	147	62.6	53	Participants were patients with first ischaemic stroke aged 18 and above who were admitted to Akdeniz University Hospital
Schultz 2017 ³⁴	Prospective cohort study; USA; 2003–2015	6051	63	64	Participants were patients who underwent cardiac catheterisation for suspected or known coronary artery disease in the Emory Cardiovascular Biobank
Sorlie 2004 ²⁵	Prospective cohort study; USA; 1973–1989	Approximately 7 000 000	≥25	–	Participants were individuals aged 25 and above in the US National Longitudinal Mortality Study
Strand 2004 ³⁷	Prospective cohort study; Norway; 1974–2000	44 684	42	50.8	Participants were individuals without history of heart disease aged 35 to 49 years in Norway
Vujcic 2014 ⁹	Prospective cohort study; Belgrade; 2002–2011	135	57.8	75.6	Participants were patients admitted to the coronary care unit of the Institute of Cardiovascular Diseases, Clinical Centre of Serbia due to MI
Wolinsky 2009 ¹⁰	Prospective cohort study; USA; 1993–2005	5511	77	38	Participants were individuals aged 70 and above in the Survey on Assets and Health Dynamics among the Oldest Old
Xie 2016 ⁷	Prospective cohort study; China; 2002–2012	1739	57.7	35.8	Participants were individuals from 11 villages in Beijing drawn from the original cohort of the People's Republic of China-United States of America Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology
Yokoyama 2014 ¹⁰	Prospective cohort study; Japan; Published in 2014	354	63	100	Participants were men who had acute MI

ACS, acute coronary syndrome; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

supplementary figure 4) and stroke mortality (OR 2.33, 95% CI 1.11 to 4.89, $I^2=0\%$, $P=0.03$, $n=1$) (online supplementary figure 6). Widowed participants of either sex in these studies did not have increased CHD mortality or stroke mortality (online supplementary figures 5 and 7).

Cardiovascular risks in general population

Unmarried participants were 1.4 times more likely to develop CVD (OR 1.42, 95% CI 1.00 to 2.01, $P=0.05$, $n=1$) (figure 3C) with a slight increase in the odds of developing CHD (OR 1.16, 95% CI 1.04 to 1.28, $I^2=69\%$, $P=0.006$, $n=8$) (figure 3A), but no difference was observed for incident stroke ($P=0.15$, $n=4$) compared with married participants (figure 3B).

Results for divorced and widowed patients is shown in table 3. Being divorced in both sexes were 1.3 times more

likely to develop CHD (OR 1.35, 95% CI 1.20 to 1.53, $I^2=0\%$, $P<0.001$, $n=3$) (online supplementary figure 10) with a slight increase in incident stroke odds (OR 1.15, 95% CI 1.01 to 1.29, $I^2=53\%$, $P=0.02$, $n=4$) (online supplementary figure 12). In contrast, widowed participants were more likely to develop a stroke (OR 1.16, 95% CI 1.09 to 1.23, $I^2=0\%$, $P<0.001$, $n=4$) (online supplementary figure 13) but not CHD ($P=0.07$, $n=1$) (online supplementary figure 11).

Mortality in CVD population (MI and stroke)

Results for participants with CVD, for the whole population and stratified by gender are summarised in figure 4 and table 4. Mortality was significantly higher for unmarried patients who sustained a myocardial infarction (OR 1.42, 95% CI 1.14 to 1.76, $I^2=83\%$, $P<0.002$, $n=11$) (figure 4A). Being divorced is

Table 2 Follow-up and results

Study ID	Population	Follow-up	Results
Akimova 2014 ²⁵	General population	12 years	CV mortality in men vs married: lonely aOR 3.19 (1.22 to 8.34) vs widowed aOR 3.18 (1.90 to 5.34); CV mortality in women vs married: lonely aOR 0.17 (0.01 to 1.09) vs widowed aOR 0.37 (0.10 to 1.04) vs divorced aOR 0.17 (0.03 to 0.84); CV mortality in men vs not married: married aOR 0.28 (0.18 to 0.44); CV mortality in women compared with not married: married aOR 3.21 (1.28 to 8.06)
Andersen 2011 ¹¹	Post-ischaemic stroke	30 day and 1 year	All-cause mortality for single vs living with someone: 30 day mortality OR 1.02 (0.78 to 1.35), 1 year OR 1.14 (0.96 to 1.34)
Bell 2013 ³⁶	Post-stroke	12–17 years	Mortality in not married vs married: aHR 0.95 (0.77 to 1.16)
Consegra-Sanchez 2015 ⁵	Post-MI	Median 6.1 years	All-cause mortality in widowed vs married: aHR 1.29 (1.13 to 1.47); All-cause mortality in single vs married: aHR 1.04 (0.79 to 1.35); All-cause mortality in divorced vs married: aHR 0.84 (0.43 to 1.38)
Digne 2015 ¹⁹	General population	18 years	Acute MI in men vs continuously married: divorced aHR 1.27 (0.98 to 1.65); remarried aHR 1.13 (0.96 to 1.34); Acute MI in women compared with continuously married: divorced aHR 1.36 (1.04 to 1.78); remarried aHR 1.35 (1.07 to 1.70)
Digne 2016 ²⁰	Post-MI	18 years	Crude results only see online supplements
Eaker 2007 ²⁷	General population	10 years	Incident CHD in men in married vs not married: aRR 0.92 (0.51 to 1.65); Incident CHD in women in married vs not married: aRR 0.85 (0.43 to 1.70); Mortality in men in married vs not married: aRR 0.54 (0.35 to 0.83); Mortality in women in married vs not married: aRR 1.04 (0.62 to 1.74)
Engstrom 2000 ¹⁴	General population	10.7 years	Cardiac events in single vs married: aHR 1.05 (0.69 to 1.6)
Engstrom 2004 ²⁸	General population	>10 years	Stroke incidence in men vs married: divorced aHR 1.29 (1.15 to 1.44); widowed aHR 1.13 (0.95 to 1.28); never married aHR 0.89 (0.77 to 1.02); Stroke incidence in women vs married: divorced aHR 1.22 (1.09 to 1.37); widowed aHR 1.13 (1.02 to 1.24); never married has no result
Engstrom 2006 ²⁰	General population	18.7 years	Coronary events vs married: never married aHR 1.29 (1.00 to 1.7); divorced aHR 1.51 (1.2 to 1.9); widowed aHR 1.78 (0.94 to 3.3); Stroke vs married: never married aHR 1.25 (0.8 to 1.9); divorced aHR 1.44 (0.98 to 2.1); widowed aHR 1.18 (0.3 to 4.8)
Flood 2014 ¹³	General population	8.8 years	IHD in partnered vs not partnered women: aRR 0.99 (0.96 to 1.02); IHD mortality in partnered vs not partnered women: aRR 0.72 (0.66 to 0.80)
Gerward 2010 ⁷	Post-coronary event	21 years	Mortality post coronary event in men vs married: never married aOR 2.14 (1.63 to 2.81); divorced aOR 1.91 (1.50 to 2.43); widowed aOR 1.49 (0.77 to 2.89); Mortality post coronary event in women vs married: never married aOR 2.32 (0.93 to 5.81); divorced aOR 1.87 (1.04 to 3.36); widowed aOR 2.74 (1.03 to 7.28)
Ghosh-Swamy 2016 ³⁸	Post-MI	15 months	Mortality vs married/common law and living together: never married aOR 1.09 (0.30 to 3.91); separated/divorced/widowed aOR 0.64 (0.24 to 1.68); MACE vs married/common law and living together: never married aOR 1.31 (0.79 to 2.16); separated/divorced/widowed aOR 0.77 (0.30 to 1.23); MI vs married/common law and living together: never married aOR 1.51 (0.68 to 3.38); separated/divorced/widowed aOR 1.02 (0.49 to 2.16); Stroke vs married/common law and living together: never married aOR 1.51 (0.68 to 3.38); separated/divorced/widowed aOR 1.02 (0.49 to 2.16); Stroke vs married/common law and living together: never married aOR 4.06 (0.91 to 18.14); separated/divorced/widowed aOR 0.60 (0.10 to 3.49)
Golbourt 2010 ³⁶	Male working adults	34 years	Fatal stroke in unmarried vs married men: aHR 1.64 (1.18 to 2.30)
Heidi 2012 ²	Post-ACS	1 year	In-hospital mortality vs married: single aOR 1.35 (0.46 to 3.99); widowed aOR 1.97 (1.23 to 3.18)
Ikeids 2009 ¹⁷	General population	Median 11 years	CHD in men for alone vs spouse: aHR 1.23 (0.74 to 2.02); CHD mortality in men for alone vs spouse: aHR 1.43 (0.73 to 2.81); All-cause mortality in men for alone vs spouse: aHR 1.47 (1.26 to 1.72); CHD in women for alone vs spouse: aHR 1.77 (0.92 to 3.39); CHD mortality in women for alone vs spouse: aHR 2.72 (1.37 to 5.38); All-cause mortality in women for alone vs spouse: aHR 1.09 (0.92 to 1.31)
Janzon 2004 ²⁴	General population	14 years	Cardiac events in women not married vs married never smoked: never smoked aRR 0.8 (0.4 to 1.7); ex-smoker aHR 1.5 (0.7 to 3.3) and current smokers aRR 5.0 (3.3 to 7.6); Cardiac events in women married vs married never smoked: ex-smoker aRR 1.4 (0.8 to 2.4); current smoker aHR 4.7 (3.2 to 6.9)
Jayaram 2013 ³⁹	Post-MI	2 years	Crude results only see online supplements
Kilpi 2015 ⁶	General population	12 years	MI events vs marital partner in men: cohabitation aHR 1.16 (1.04 to 1.30) living with others aHR 1.10 (0.99 to 1.21); living alone aHR 1.18 (1.08 to 1.28); MI events vs marital partner in women: cohabitation aHR 1.08 (0.85 to 1.37) living with others aHR 1.19 (0.97 to 1.45) living alone aHR 1.16 (0.99 to 1.36); Mortality in MI vs marital partner in men: cohabitation aHR 1.07 (0.86 to 1.33) living with others aHR 1.30 (1.06 to 1.60) living alone aHR 1.06 (0.80 to 1.40)
Kriegbaum 2008 ³⁵	General population	12 years	IHD in men vs cohabitant: never cohabitant aHR 0.89 (0.62 to 1.30); broken partnership aHR 1.28 (1.03 to 1.59)
Malyudina 2004 ⁸	General population	10.3 years	All-cause mortality in men vs married: non-married aHR 1.28 (1.00 to 1.64); single aHR 1.36 (0.87 to 2.11); divorced aHR 1.43 (1.02 to 2.00); widowed aHR 0.87 (0.50 to 1.52); CVD mortality in men vs married: non-married aHR 1.22 (0.84 to 1.77); single aHR 0.89 (0.38 to 2.01); divorced aHR 1.78 (1.13 to 2.82); widowed aHR 0.61 (0.25 to 1.50); CHD mortality in men vs married: non-married aHR 1.20 (0.74 to 1.95); single aHR 0.62 (0.19 to 1.99); divorced aHR 1.84 (1.04 to 3.26); widowed aHR 0.77 (0.24 to 2.44); Stroke mortality in men vs married: non-married aHR 1.19 (0.56 to 2.49); single aHR 0.81 (0.11 to 5.85); divorced aHR 2.40 (1.03 to 5.58); All-cause mortality in women vs married: non-married aHR 1.37 (0.92 to 2.04); single aHR 0.99 (0.31 to 3.18); divorced aHR 1.86 (1.07 to 3.24); widowed aHR 1.16 (0.70 to 1.93); CVD mortality in women vs married: non-married aHR 1.15 (0.67 to 1.97); single aHR 0.62 (0.08 to 4.59); divorced aHR 1.41 (0.63 to 3.18); widowed aHR 1.05 (0.54 to 2.04); CHD mortality in women vs married: non-married aHR 1.14 (0.55 to 2.39); single aHR 1.25 (0.16 to 9.55); divorced aHR 1.44 (0.49 to 4.26); widowed aHR 1.00 (0.40 to 2.50); Stroke mortality in women vs married: non-married aHR 1.52 (0.53 to 4.33); divorced aHR 2.11 (0.45 to 9.82); widowed aHR 1.44 (0.42 to 4.99)
Masello 2009 ³¹	General population	9.4 years	Incident stroke in men vs married: divorced/separated aHR 1.01 (0.79 to 1.29); never married aHR 1.15 (0.80 to 1.67); widowed aHR 1.23 (0.99 to 1.53); Incident stroke in women vs married: divorced/separated aHR 0.95 (0.77 to 1.16); never married aHR 1.27 (0.95 to 1.69); widowed aHR 1.11 (0.97 to 1.28)
Mathews 2002 ²⁹	General population	9 years	Mortality vs married: separated aHR 1.24 (0.98 to 1.57); divorced aHR 1.37 (1.09 to 1.72); Cardiovascular mortality vs married: separated aHR 1.43 (1.05 to 1.96); divorced aHR 1.40 (1.01 to 1.92); CHD mortality vs married: separated aHR 1.02 (0.67 to 1.57); divorced aHR 1.66 (1.17 to 2.36); MI mortality compared with married: separated aHR 1.31 (0.76 to 2.26); divorced aHR 1.15 (0.64 to 2.06)
Orth-Gomér 2000 ³²	Post-ACS	5 years	Crude results only see online supplements
Panagiotakos 2008 ⁸	Post-ACS	30 days	Mortality in married vs never married aOR 2.70 (1.82 to 3.99); widowed/divorced aOR 1.21 (0.42 to 3.53); CVD compared with married: never married aOR 1.07 (0.41 to 2.82); widowed/divorced aOR 1.21 (0.42 to 3.53)
Quinones 2014 ³³	Post-MI	Median 5.3 years	Mortality in married vs not married: aHR 0.83 (0.68 to 1.01)
Sarnanci 2004 ¹²	Post-stroke	1 year	Mortality in single/widowed vs married: OR 2.03 (1.22 to 8.51)
Schultz 2017 ³⁴	Post-cardiac catheterisation or CHD	Median 3.7 years	Mortality vs married: unmarried aHR 1.14 (0.95 to 1.37); divorced aHR 1.23 (0.98 to 1.55); widowed aHR 1.24 (0.99 to 1.54); Cardiovascular death vs married: unmarried aHR 1.33 (1.06 to 1.68); divorced aHR 1.27 (0.95 to 1.69); widowed aHR 1.62 (1.23 to 2.13); Cardiovascular death and MI vs married: unmarried aHR 1.46 (1.22 to 1.76); divorced aHR 1.41 (1.10 to 1.81); widowed aHR 1.71 (1.32 to 2.20)
Serite 2004 ²⁵	General population	Up to 11 years	Out-of-hospital all-cause death in not married vs married: aOR 1.33 (1.28 to 1.38); Out-of-hospital CHD death in not married vs married: aOR 1.60 (1.50 to 1.71)
Strand 2004 ²⁷	General population	23.6 years	IHD death in men vs married: not married aHR 1.28 (1.12 to 1.46); divorced/separated aHR 1.21 (0.84 to 1.76); widowed aHR 0.28 (0.07 to 1.14); IHD death in women vs married: not married aHR 1.33 (0.85 to 2.09); divorced/separated aHR 1.35 (0.69 to 2.63); widowed aHR 0.87 (0.43 to 1.76)
Vujcic 2014 ⁹	Post-MI	Median 77 months	Mortality in others vs married: OR 2.38 (1.14 to 4.98); Mortality in living alone vs not alone: aOR 7.60 (1.99 to 29.08)
Wolinsky 2009 ⁴⁰	Elderly population	12 years	Crude results only see online supplements
Xie 2016 ²	General population	10 years	Crude results only see online supplements
Yokoyama 2014 ¹⁰	Post-MI	1.7 years	Mortality unmarried vs married: aHR 3.84 (1.22 to 10.2)

ACS, acute coronary syndrome; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; IHD, ischaemic heart disease; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3 Risk of adverse outcomes considering marital status in the general population

Outcome	Marital status and subgroups	Studies	No. of participants (not applicable, (NA) for studies with no crude result available)	Odds ratio (95% CI)	Overall effect, P values	Heterogeneity, I ² %	Subgroup differences between men only and women only (P values, I ²)
CHD death	Unmarried vs married						
	All	5	>766 272 (2 NA)	1.43 (1.28 to 1.60)	<0.001	57	
	Men only	3	>16 137 (1 NA)	1.28 (1.13 to 1.45)	<0.001	0	0.35, 0%
	Women only	4	>750 135 (1 NA)	1.44 (1.16 to 1.78)	<0.001	25	
	Men and women	1	NA	1.60 (1.50 to 1.71)	<0.001	–	
	Divorced vs married						
	All	3	>10 378 (2 NA)	1.33 (1.04 to 1.70)	0.02	0	
	Men only	3	>6139 (2 NA)	1.32 (1.00 to 1.73)	0.05	0	0.90, 0%
	Women only	2	>4239 (1 NA)	1.37 (0.78 to 2.43)	0.27	0	
	Widowed vs married						
	All	2	>10 105 (1 NA)	0.78 (0.48 to 1.25)	0.29	0	
	Men only	2	>5940 (1 NA)	0.50 (0.19 to 1.34)	0.17	16	0.30, 8.7%
Women only	2	>4165 (1 NA)	0.92 (0.52 to 1.60)	0.76	0		
Separated vs married							
Men only	1	10 330	1.31 (0.76 to 2.26)	0.33	–		
Stroke death	Unmarried vs married						
	All	2	>11 404 (1 NA)	1.55 (1.16 to 2.08)	0.003	0	
	Men only	2	>6485 (1 NA)	1.55 (1.15 to 2.11)	0.005	0	0.97, 0%
	Women only	1	4919	1.52 (0.53 to 4.34)	0.43	–	
	Divorced vs married						
	All	1	10 724	2.33 (1.11 to 4.89)	0.03	0	
	Men only	1	6485	2.40 (1.03 to 5.59)	0.04	–	0.89, 0%
	Women only	1	4239	2.11 (0.45 to 9.86)	0.34	–	
	Widowed vs married						
	All	1	10 105	1.09 (0.39 to 3.09)	0.86	0	
	Men only	1	5940	0.55 (0.08 to 3.85)	0.55	–	0.41, 0%
	Women only	1	4165	1.44 (0.42 to 4.92)	0.56	–	
CVD death	Unmarried vs married						
	All	2	>11 404 (1 NA)	1.20 (0.55 to 2.65)	0.65	89	
	Men only	2	>6485 (1 NA)	2.07 (0.72 to 5.94)	0.17	92	0.16, 49.4%
	Women only	2	>4919 (1 NA)	0.63 (0.18 to 2.26)	0.48	83	
	Divorced vs married						
	All	3	>20 769 (1 NA)	1.56 (0.95 to 2.56)	0.08	73	
	Men only	3	>16 530 (1 NA)	1.93 (1.22 to 3.06)	0.005	71	0.25, 24.7%
	Women only	2	>4239 (1 NA)	0.56 (0.07 to 4.37)	0.58	80	
	Widowed vs married						
	All	2	>10 105 (1 NA)	0.96 (0.43 to 2.16)	0.93	69	
	Men only	2	>5940 (1 NA)	1.38 (0.27 to 6.99)	0.70	84	0.48, 0%
	Women only	2	>4165 (1 NA)	0.70 (0.26 to 1.90)	0.48	57	
Separated vs married							
Men only	1	10 330	1.43 (1.05 to 1.95)	0.02	–		
All-cause mortality	Unmarried vs married						
	All	4	>33 145 (2 NA)	1.31 (1.19 to 1.45)	<0.001	42	
	Men only	3	>16 137 (1 NA)	1.45 (1.26 to 1.66)	<0.001	11	0.01, 83.3%
	Women only	3	>17 008 (1 NA)	1.12 (0.96 to 1.30)	0.16	0	
	Men and women	1	NA	1.33 (1.28 to 1.38)	<0.001	–	
	Divorced vs married						
	All	2	>10 378 (1 NA)	1.43 (1.20 to 1.71)	<0.001	0	
	Men only	2	>6139 (1 NA)	1.39 (1.15 to 1.68)	<0.001	0	0.33, 0%
	Women only	1	4239	1.86 (1.07 to 3.24)	0.03	–	
	Widowed vs married						
	All	1	10 105	1.02 (0.70 to 1.48)	0.93	0	
	Men only	1	5940	0.87 (0.50 to 1.52)	0.62	–	0.45, 0%
Women only	1	4165	1.16 (0.70 to 1.93)	0.57	–		
Separated vs married							
Men only	1	NA	1.24 (0.98 to 1.57)	0.07	–		
CVD events	Unmarried vs married						
	Men and women	1	1739	1.42 (1.00 to 2.01)	0.05	–	

Continued

Table 3 Continued

Outcome	Marital status and subgroups	Studies	No. of participants (not applicable, (NA) for studies with no crude result available)	Odds ratio (95% CI)	Overall effect, P values	Heterogeneity, I ² %	Subgroup differences between men only and women only (P values, I ²)
CHD events	Unmarried vs married						
	All	8	>1 011 397 (2 NA)	1.16 (1.04 to 1.28)	0.006	69	
	Men only	5	>134 152 (2 NA)	1.21 (1.14 to 1.30)	<0.001	0	0.20, 40.2%
	Women only	5	>867 894 (2 NA)	1.10 (0.96 to 1.26)	0.19	41	
	Men and women	1	9351	1.05 (0.69 to 1.60)	0.82	–	
	Divorced vs married						
	All	3	>12 812 (1 NA)	1.35 (1.20 to 1.53)	<0.001	0	
	Men only	3	>5389 (1 NA)	1.35 (1.18 to 1.55)	<0.001	0	0.97, 0%
	Women only	1	NA	1.36 (1.04 to 1.78)	0.02	–	
	Widowed vs married						
	Men only	1	4754	1.78 (0.95 to 3.34)	0.07	–	
	Remarried vs married						
All	1	NA	1.21 (1.02 to 1.44)	0.03	33		
Men only	1	NA	1.13 (0.96 to 1.34)	0.15	–	0.22, 33.1%	
Women only	1	NA	1.35 (1.07 to 1.70)	0.01	–		
Stroke events	Unmarried vs married						
	All	4	>19 829 (2 NA)	1.23 (0.93 to 1.63)	0.15	78	
	Men only	3	>8640 (2 NA)	1.01 (0.81 to 1.26)	0.93	41	0.21, 35%
	Women only	1	8268	1.27 (0.95 to 1.69)	0.10	–	
	Men and women	1	2921	1.93 (1.34 to 2.78)	<0.001	–	
	Divorced vs married						
	All	4	>26 843 (1 NA)	1.15 (1.02 to 1.29)	0.02	53	
	Men only	3	>14 532 (1 NA)	1.22 (1.02 to 1.46)	0.03	46	0.47, 0%
	Women only	2	>9279 (1 NA)	1.09 (0.86 to 1.39)	0.47	77	
	Men and women	1	3032	0.94 (0.62 to 1.43)	0.77	–	
	Widowed vs married						
	All	4	>29 692 (1 NA)	1.16 (1.09 to 1.23)	<0.001	0	
	Men only	3	>13 728 (1 NA)	1.16 (1.03 to 1.29)	0.01	0	0.69, 0%
	Women only	2	>10 948 (1 NA)	1.12 (1.04 to 1.22)	0.004	0	
	Men and women	1	5016	1.33 (1.12 to 1.57)	<0.001	–	

CHD, coronary heart disease; CVD, cardiovascular disease.

not associated with increased mortality after MI ($P=0.13$, $n=3$) (figure 4B). For widowed participants, the increased odds of death post-MI was almost 1.7 times (OR 1.68, 95% CI 1.30 to 2.17, $I^2=85\%$, $P<0.001$, $n=4$) (figure 4C).

After a stroke, there was no difference in mortality between unmarried and married participants ($P=0.47$, $n=3$) (online supplementary figure 14).

Mortality in post-cardiac catheterisation population

In the post-cardiac catheterisation population consisting of a heterogeneous cohort of patients under elective investigation for possible coronary artery disease or acutely following a myocardial infarction, there was no significant difference in all-cause mortality in the unmarried, divorced and widowed groups when compared with married participants with adjusted hazard ratio (aHR) 1.14 (95% CI 0.95 to 1.37), aHR 1.23 (95% CI 0.98 to 1.55), and aHR 1.24 (95% CI 0.99 to 1.54), respectively. Both the unmarried and widowed participants were at increased risk of cardiovascular death, corresponding aHR 1.33 (95% CI 1.06 to 1.68) and aHR 1.62 (95% CI 1.23 to 2.13), respectively, but the risk was not significant in divorced participants (aHR 1.27, 95% CI 0.95 to 1.69).

DISCUSSION

To the best of our knowledge, this is the first evidence synthesis to quantify the evidence base using meta-analysis to evaluate the relationship between marital status and cardiovascular disease. Our analysis showed that compared with married individuals,

being unmarried was associated with increased CHD and both CHD and stroke mortality in the general population. Similarly, we observed greater odds of death from CHD and stroke in divorced compared with married individuals. Finally, in the widowed population only stroke incidence was elevated with similar odds in both sexes. Our analysis also describes important differences in prognosis with regard to mortality according to marital status in patients with incident cardiovascular disease. In participants who suffered a myocardial infarction, being unmarried was associated with greater odds of mortality compared with a married individual, with a non-significant trend in widowed or divorced individuals. In our analysis, no significant gender effect was observed for the association between marital status and developing CVD and death from CVD in any groups of participants, although differences in total mortality were noted.

We have built on the current understanding of marital status and adverse outcomes in several ways. First, a previous meta-analysis of 53 studies demonstrated higher all-cause mortality in never married, divorced and widowed married versus married individuals,⁴¹ but the study did not explore any specific causes of death or cardiovascular disease. A more recent review published by Manfredini *et al* describes the improved health status and reduced cardiovascular risk with married status but it did not quantify the relationships with meta-analysis.⁴² Our updated review with 34 studies has built on the findings of these reviews to quantify the relationship between marital status and CVD while considering the unmarried, divorced and widowed status of the populations assessed.

Several mechanisms have been suggested to account for the observed protective effect of marital status on CVD, especially in men. Social causation theory suggests that individuals benefit from spousal support.⁴³ For example, living with another person allows earlier recognition and response to warning symptoms,^{16 25} especially if a myocardial infarction becomes instantly disabling.²⁵ Studies have reported that unmarried patients had longer delays in seeking medical help^{7 8 16 44} and longer total ischaemic times⁴⁴ which directly influences both the timing and proportion of participants being treated with either thrombolysis or invasive cardiac procedures that reduce mortality.^{7 8} In addition, spouses, particularly wives, encourage concordant health behaviour such as a healthy lifestyle^{13 16 19 45} and adherence to treatment^{5 13 16 19 45} that promote cardiovascular health. In contrast, marital dissolution is noted to affect the health behaviour mentioned above negatively.²⁹ Moreover, Wu *et al* reported that compared with married individuals, unmarried individuals were twice more likely to be non-adherent to their prescribed medications which was the strongest predictor of better outcome in their study.⁴⁵ There are greater financial resources, especially in households with a dual income, making better healthcare more accessible.^{13 16 30} Furthermore, one of the benefits of being married or with a partner may be increased participation in cardiac rehabilitation which improves outcomes after cardiovascular disease.⁴⁶

Stress-related theory suggests that partner loss or poor-quality relationships may have a negative impact on the economic, behavioural and emotional well-being of an individual which may reduce one's ability to prevent, detect and treat illness.³³ Biologically, stress may ultimately worsen cardiovascular risk factors such as hypertension, reduced

heart rate variability, impaired vagal tone, hyperlipidaemia, diabetes and the progression of atherosclerosis.^{9 29 32} The buffering hypothesis suggests that informational or emotional resources from a spouse promote adaptive behaviour and may reduce excessive neuroendocrine response to acute or chronic stressors.^{17 35} This translates into a decrease in progression of atherosclerosis and other pathological processes, thus reducing the risk of CVD.

Furthermore, selection theory has been introduced which assumes that individuals with poor health are less likely to establish or maintain long-term relationships such as marriage.^{5 33} Also, Floud *et al* suggested the possibility that healthy women may be less likely to divorce,¹³ although Akimova *et al* reported that divorced and single women were more highly educated and had a higher qualified occupation which results in greater financial independence and better quality of life.³⁵

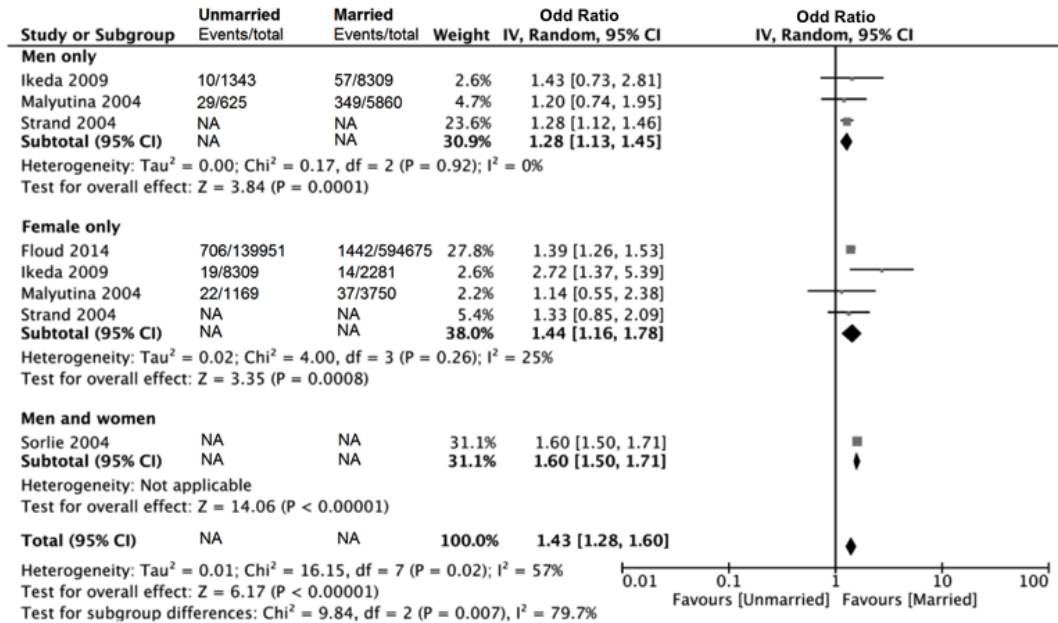
In widowed populations, there is less variation in CVD incidence and mortality between sexes with some studies showing women do more poorly than men. Vujcic *et al* showed that the proportion of women who lived alone increased with age while the proportion of men who lived alone decreased with age.⁹ Possible explanations include women tend to be younger than their husbands and have a longer life expectancy.⁹ Thus, it is postulated that widowed women tend to be older and more support is needed to meet their healthcare requirement. This study has several strengths and limitations. This is the largest study to date with a sample size of more than 2 million compared with the smaller sample sizes of previous reviews.^{41 42} We were able to quantify the risk with meta-analysis which was not performed in the previous studies.⁴² In terms of generalisability, the current review included populations from various age

Table 4 Risk of adverse outcomes considering marital status in specific groups of participants

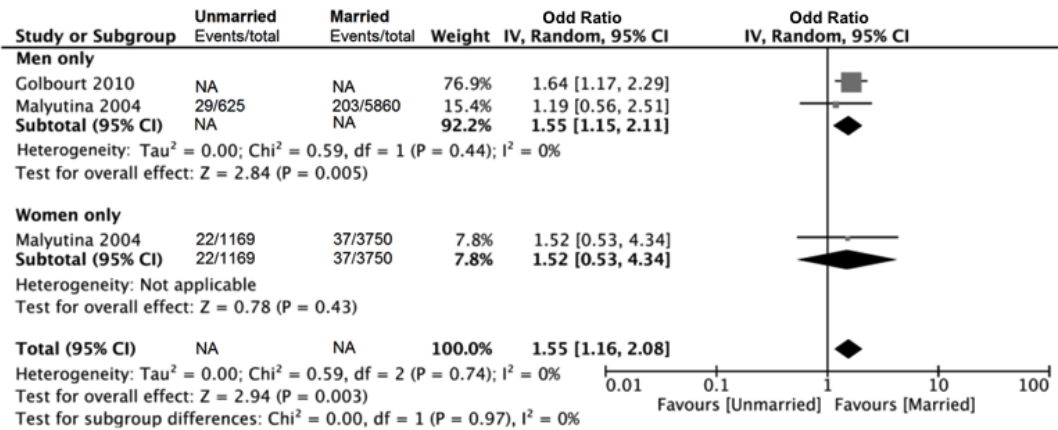
Outcome	Marital status and subgroups	Studies	No. of participants (not applicable, (NA) for studies with no crude result available)	Odds ratio (95% CI)	Overall effect, P value	Heterogeneity, I ² %	Subgroup differences between men only and women only (P value, I ²)
Mortality post stroke	Unmarried vs married						
	All	3	29 419	1.08 (0.88 to 1.32)	0.47	43	
	Women only	1	3156	0.95 (0.77 to 1.17)	0.62	–	
	Men and women	2	26 263	1.24 (0.83 to 1.84)	0.29	24	
Mortality post MI	Unmarried vs married						
	All	11	>21456 (3 NA)	1.42 (1.14 to 1.76)	0.002	83	
	Men only	2	>2453 (1 NA)	1.76 (1.24 to 2.49)	0.001	80	0.56, 0%
	Women only	2	>374 (1 NA)	1.38 (0.67 to 2.86)	0.38	61	
	Men and women	9	>18629 (2 NA)	1.35 (1.00 to 1.83)	0.05	84	
	Divorced vs married						
	All	3	>4158 (1 NA)	1.36 (0.92 to 2.01)	0.13	85	
	Men only	1	2525	1.91 (1.50 to 2.43)	<0.001	–	0.95, 0%
	Women only	1	447	1.87 (1.04 to 3.36)	0.04	–	
	Men and women	2	>1186 (1 NA)	1.08 (0.95 to 1.22)	0.23	0	
	Widowed vs married						
	All	4	>9171 (1 NA)	1.68 (1.30 to 2.17)	<0.001	85	
	Men only	1	2136	1.49 (0.77 to 2.89)	0.24	–	0.31, 2.3%
Women only	1	368	2.74 (1.03 to 7.28)	0.04	–		
Men and women	3	>6667 (1 NA)	1.65 (1.24 to 2.20)	<0.001	92		
MI post MI	Unmarried vs married						
	All	2	1964	0.72 (0.14 to 3.60)	0.69	77	
	Women only	1	222	0.29 (0.08 to 1.08)	0.07	–	
	Men and women	1	1742	1.51 (0.68 to 3.37)	0.31	–	
MACE post MI	Unmarried vs married						
Men and women	1	1742	1.31 (0.79 to 2.17)	0.29	–		
Major bleeding post MI	Unmarried vs married						
	Men and women	1	1742	2.11 (0.55 to 8.10)	0.28	–	
CVD post MI	Unmarried vs married						
	Men and women	1	1813	1.07 (0.41 to 2.81)	0.89	–	

CVD, cardiovascular disease; MACE, major adverse cardiac events; MI, myocardial infarction.

A) CHD death



B) Stroke deaths



C) CVD death

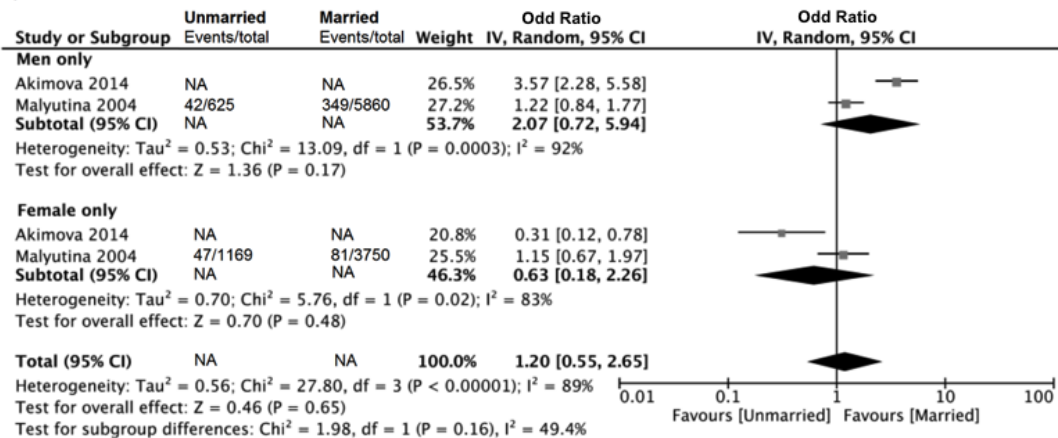
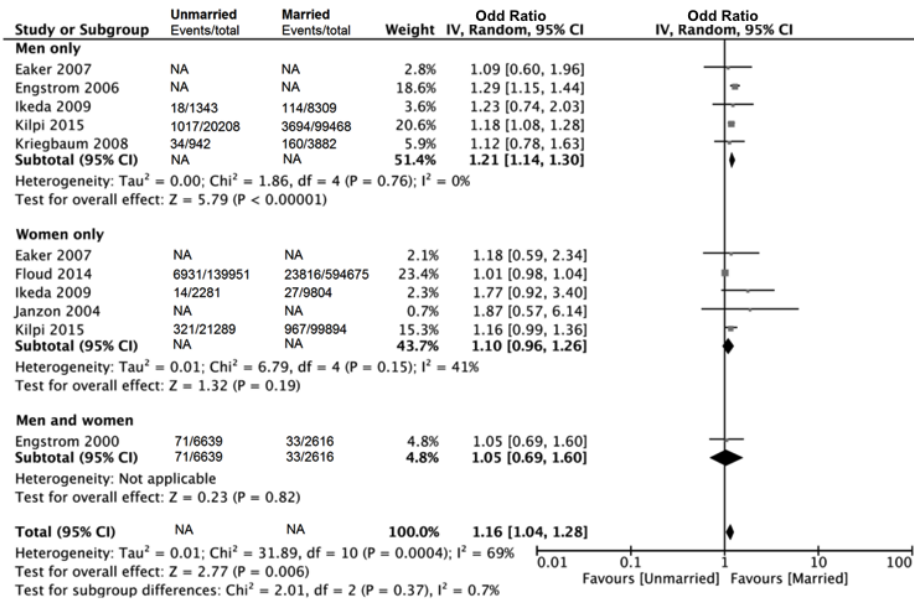
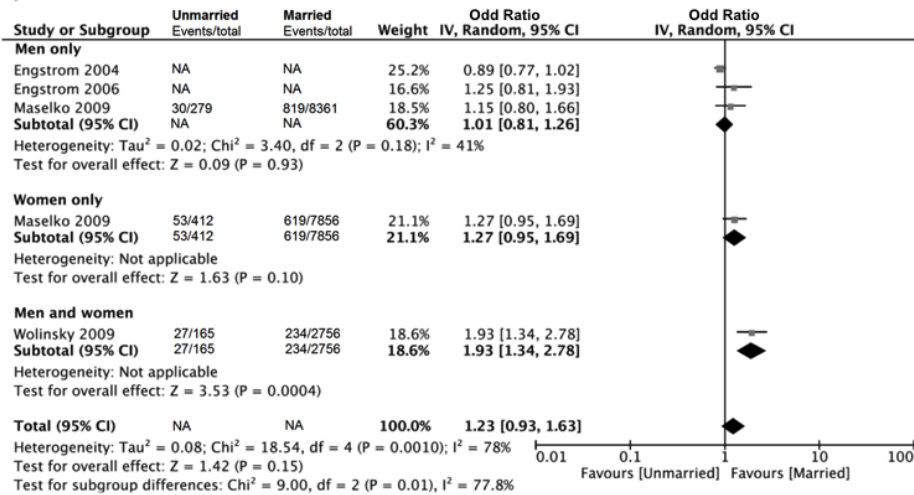


Figure 2 Forest plots of coronary heart disease (CHD), stroke and cardiovascular disease (CVD) deaths in unmarried vs married in the general population.

A) CHD events



B) Stroke events



C) CVD events

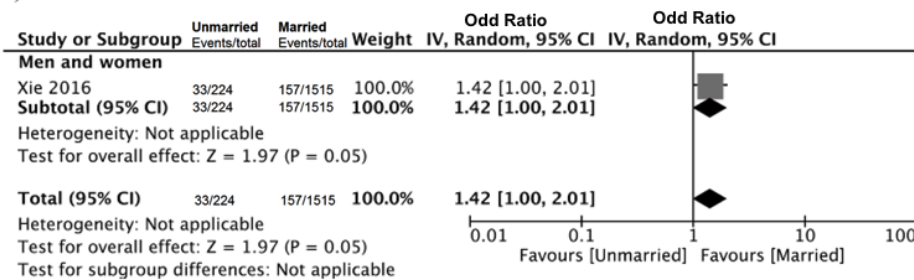
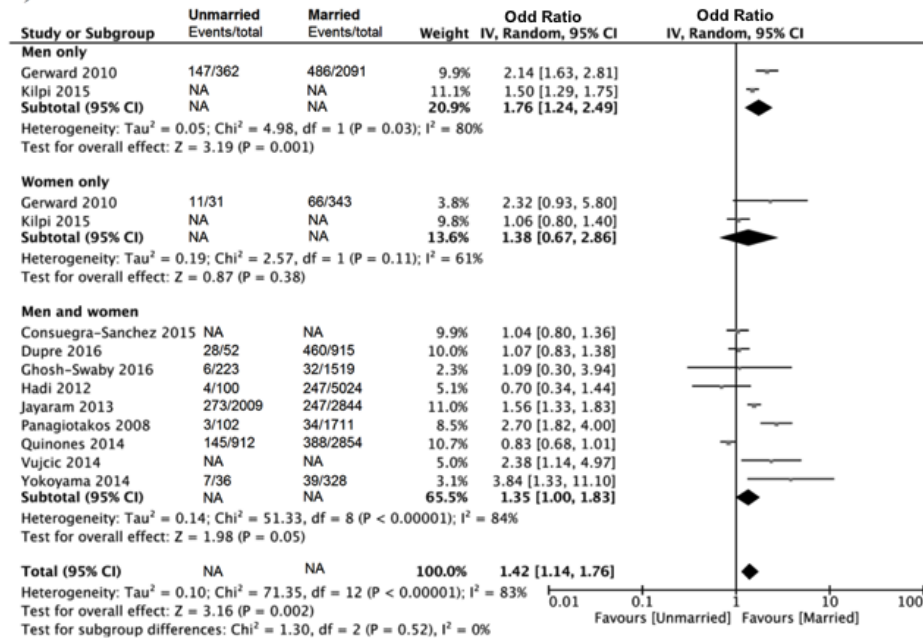


Figure 3 Forest plot of coronary heart disease (CHD), stroke and cardiovascular disease (CVD) events in unmarried vs married in the general population.

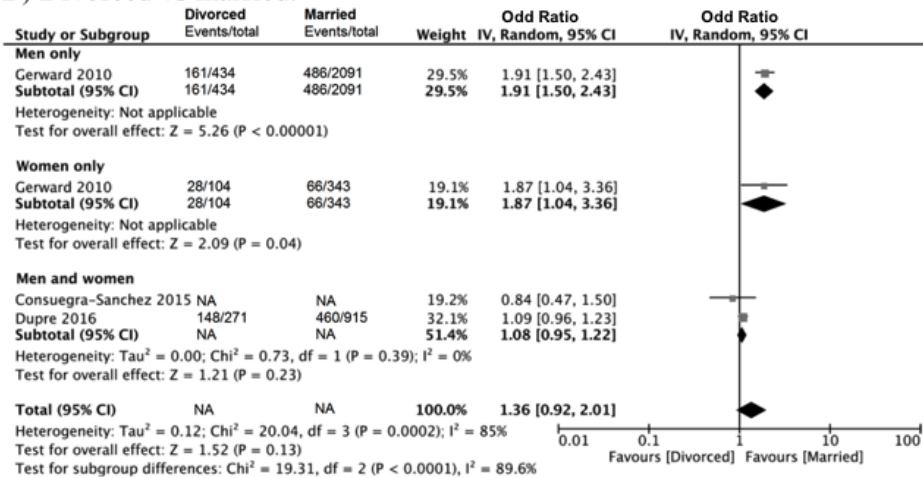
groups, ethnicities and geographic locations making the findings generalisable to different populations. We used a comprehensive search strategy of the literature and excluded case-control and retrospective studies to reduce the possibility of bias. Finally, results with the greatest extent of adjustments were used for the analysis in this study.

The major limitation of this study is the inconsistent variable adjustments across studies, which poses a risk of confounding. Adjustment for cardiovascular risk factors was often incomplete in many of the studies analysed, which may have influenced our result. In addition, this review is not an individual patient meta-analysis so information is solely derived from published

A) Unmarried vs married.



B) Divorced vs married.



C) Widowed vs married.

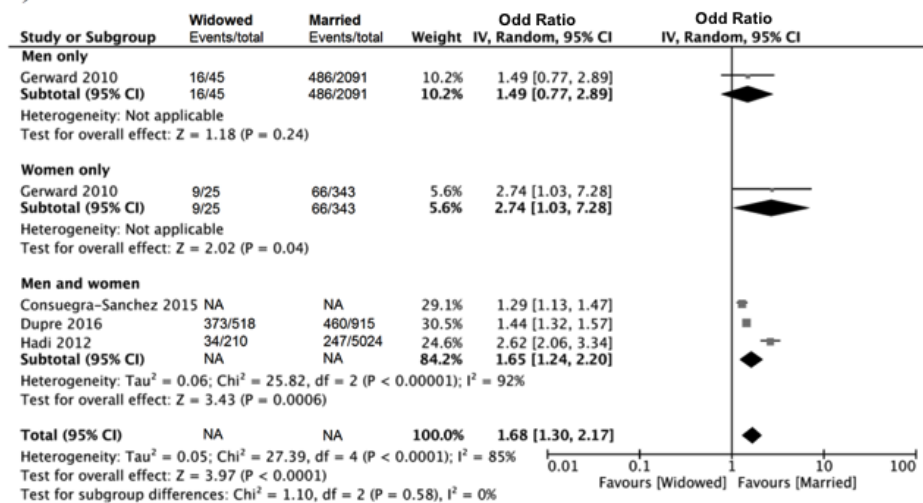


Figure 4 Forest plot of post myocardial infarction mortality by marital status.

material. The lack of information on same-sex spouses and quality of marriage limit further insight into the impact of marriage. Moreover, heterogeneity exists across studies in terms of study methodology. For example, the definition of CVD varied across the studies and the follow-up period was inconsistent with some long-term studies (>15 years of follow-up) where management might have changed over time.^{7 19 20 30 36 37}

Future work should focus on whether marital status is a surrogate marker of other adverse health behaviour or cardiovascular risk profiles that underlies our reported findings and whether targeted interventions should focus on such high-risk groups. The association between cohabitation/living with someone and CVD should be explored as it may be a confounding factor in this study. In Quinones *et al*, the replacement of marital status with cohabitation yielded the same protective effect although slightly less pronounced.³³ Fournier *et al* suggested that having information of 'living alone' versus 'living with someone' instead of married versus not married would have been more useful.⁴³

In conclusion, being married appears to be associated a lower cardiovascular mortality and incidence of CVD in a general population and mortality after myocardial infarction. While current evidence may demonstrate an association between marital status and mortality and CVD, lack of social support might be a mitigating factor. Future research should focus around whether marital status is a surrogate marker for other adverse health behaviour or cardiovascular risk profiles that underlies our reported findings, or whether marital status should be considered as a risk factor by itself.

Key questions

What is already known about this subject?

- ▶ While 80% of the risk for future cardiovascular disease (CVD) can be predicted from known cardiovascular risk factors such as hypertension, smoking and diabetes mellitus, the determinants for the remaining 20% risk remain unclear.
- ▶ One factor which may be associated with CVD is marital status and studies have reported inconsistent findings.

What does this study add?

- ▶ Our analysis showed that compared with married individuals, being unmarried was associated with increased all cause mortality, coronary heart disease (CHD) and both CHD and stroke mortality in the general population.
- ▶ Similarly, we observed a greater odds of death from CHD and stroke in divorced compared with married individuals.
- ▶ In the widowed population only stroke incidence was elevated with similar odds in both sexes.

How might this impact on clinical practice?

- ▶ These findings may suggest that marital status should be considered in the risk assessment for CVD.

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Contributors MAM and CSK conceived and planned the study. CSK and CWW performed the search for relevant studies. Data were screened, extracted and analysed by CSK and CWW. CWW wrote the first draft of the paper. All authors contributed to the interpretation of the findings and critically revised it for intellectual content.

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