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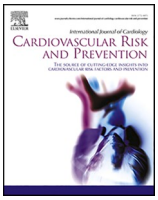
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A systematic review comparing cardiovascular disease among informal carers and non-carers

Ameer Lambrias *, Jennifer Ervin, Yamna Taouk, Tania King

Melbourne School of Population and Global Health, The University of Melbourne, Australia

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ABSTRACT

Exposure to chronic stress increases the risk of cardiovascular disease (CVD). Providing informal care is known to be a stressful activity, but it is not clear whether informal caregiving is associated with CVD risk. This systematic review aimed to summarise and assess the quantitative evidence examining the association between providing informal care to others and CVD incidence in comparison with non-carers. Eligible articles were detected by searching six electronic literature databases (CINAHL, Embase, Global Health, OVID Medline, Scopus, and Web of Science). Two reviewers appraised 1887 abstracts and 34 full-text articles against a set of a priori eligibility criteria to identify articles for inclusion. Quality assessment of included studies was performed using the ROBINS-E risk of bias tool. Nine studies were identified that quantitatively assessed the association between providing informal care and CVD incidence in comparison to not providing informal care. Overall, there was no difference in the incidence of CVD between carers and non-carers across these studies. However, within the subgroup of studies that examined care provision intensity (hours/week) higher CVD incidence was observed for the most intense caregiving group compared to non-carers. One study examined only CVD-related mortality outcomes, observing a reduction in mortality for carers compared to non-carers. More research is required to explore the relationship between informal care and CVD incidence.

1. Introduction

Unpaid informal care represents a valuable societal resource to assist and meet the needs of vulnerable people, while also reducing demands and cost burdens on formal health institutions. Indeed, the work performed by informal carers in Australia has been estimated to be worth about AU$78 billion, which is equivalent to 4% of the country's total GDP [1]. On a global scale, informal care is estimated to account for 16.4 billion hours of unpaid care work each day [2].

Compared with people who do not provide care to others, informal carers report having reduced time for leisure and self-care activities [3]. They also face the additional financial costs that come with supporting the needs of a person who cannot independently sustain themselves [4]. Moreover, the demands of informal care can significantly compromise carers' capacity to perform and be available for paid employment [5].

Key social determinants affect the likelihood of an individual performing unpaid care work, with gender, age and socioeconomic status all having an influence [6]. In the UK, the rate of caregiving increases with age up to the 45–59 year age group and females are more likely to provide care than males in all age groups below 70 years and over [7]. It is estimated that 84% of carers worldwide are female and that 92% experience financial insecurity [8].

In contrast with paid care workers, informal carers typically have an existing relationship with their care recipient [9]. For people who provide care to a relative, prior studies have observed a 'family effect' of caregiving [10]. This family effect links the wellbeing of the family carer with the welfare of their care recipient [11], whereby the stress of caregiving can be exacerbated based on the condition of their kin care recipient. Research examining this family effect reports that family carers suffered adverse mental health effects as the health of their parents or spouses deteriorated [12,13]. The quality of the relationship between informal carer and care recipient can also impact on the health of each person. An integrative review found that high quality relationships yielded benefits for both informal carers and care recipients, with reduced distress and caregiving burden observed among carers who had high quality relationships with their care recipients [14].

Health-related effects that have been associated with informal caregiving include increases in cardiovascular disease risk factors such

Abbreviations: CVD, Cardiovascular Disease.

* Corresponding author.
E-mail address: alambrias@student.unimelb.edu.au (A. Lambrias).

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as hypertension [15], depressive symptoms [16], and Framingham CVD risk scores [17]. Conversely, in some studies, reduced mortality has been observed for caregivers versus non-caring controls [18,19]. It has been posited by Fredman et al. [18] that this association can be explained by the 'healthy-caregiver effect', a form of selection bias which is an analogue of the healthy worker effect. The healthy-caregiver effect suggests that people who provide care must be relatively healthy in comparison with the general population, including people who are in poor health and are therefore less likely to act as a caregiver to others.

Informal care and CVD were first found to be associated in a study by Vitaliano et al. [20]. The researchers hypothesised that by inducing chronic stress, caring for a spouse could trigger sequential events resulting in the onset of coronary heart disease (CHD) [20]. This path model theorises that chronic caregiving stress leads to distress and poor health behaviours, both of which are associated with metabolic syndrome which, in turn, can manifest as CHD [20]. Moreover, they postulated that this pathway could be modified by an individual's vulnerability, defined in the study as anger and hostility, as well as their personal and social resources, including socioeconomic position and social support [20].

Four previous reviews have examined the relationship between informal care and CVD. An epidemiologic review of the health of carers of older adults by Capistrant [21] reported two studies had observed increases in cardiovascular disease incidence among caregivers who had provided care for at least either 9 or 14 hours per week. Subsequent reviews by Bouchard et al. [22] and Xu et al. [23]. Investigated risk factors for CVD (rather than incidence). One reported that the relationship quality between caregiver and care-recipient was an effect modifier of the association between caregiving and CVD risk [22], and another found that caregiving for family members with dementia was a non-modifiable risk factor associated with CVD risk [23].

A recent systematic review by Ahn et al. [24] explored both CVD incidence and risk amongst family caregivers of adults with chronic conditions. This review included six studies which explored an association between caregiving and outcomes of CVD incidence. In five out of these six studies, Ahn et al. [24] noted that increases in CVD outcomes were observed among caregivers, specifically among those who either provided care for more than a certain number of hours per week, were more stressed, or had poorer self-rated mental or physical health. In addition, Ahn et al. [24] identified 35 studies that measured CVD risk through hypertension, metabolic syndrome, risk scores, subclinical markers, or biochemical markers. In synthesising the evidence across these studies, Ahn et al. [24] concluded that carers were more likely to have higher CVD incidence and risk in comparison to non-carers.

Prior reviews examining informal care and cardiovascular health have focused primarily on the risk factors of CVD, rather than incident cases of disease and these reviews also typically imposed a restriction on the eligible caregiver population based on the condition of the person receiving informal care. This review sets itself apart from prior work by addressing specific research gaps. Firstly, we assess incidence of cardiovascular disease as the outcome, rather than risk factors. Secondly, unpaid informal carers of any vulnerable population were eligible for inclusion. And lastly, restricted our review to studies that had a non-caring comparator group. These criteria allow this review to capture studies that have maximised their ability to make causal inferences regarding the association of interest whilst drawing from the widest breadth of the caregiving literature to be included and assessed.

The main aims of this review are.

- To summarise the quantitative evidence examining the association between providing informal unpaid caregiving and cardiovascular disease incidence in comparison with non-caregivers.
- To assess the quality of the existing evidence.

2. Methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [25] and was registered with PROSPERO on the International Prospective Register of Systematic Reviews (ID: CRD42022328638).

A two-tiered search strategy was developed to identify relevant studies. The first tier comprised terms that related to informal care, using truncation to maximise the breadth of results. This was combined using Boolean operators with a second tier, consisting of terms related to CVD outcomes; truncation was also used in this tier to improve the accuracy of the search. Searches were conducted on the March 31, 2022 across six electronic databases: CINAHL, Embase, Global Health, OVID Medline, Scopus, and Web of Science (See Appendix 1 for search strategy). References of included studies were also screened to identify relevant papers.

The review was restricted to full-text quantitative studies using any observational design that examined the association between informal care provision and CVD outcomes. Qualitative studies, reviews, and case studies were not eligible in this review. The eligible study population included adults over 18 years of age. Exposure status was defined as being identified as an individual who provided any form of unpaid informal care to vulnerable or dependent persons (inclusive of children, people with disability, people in a state of mental or physical illness, and the elderly).

Studies of individuals who had been observed to have CVD before their caregiving status was ascertained were deemed ineligible. Eligible CVD outcomes included myocardial infarction, coronary heart disease, cerebrovascular disease, peripheral arterial disease, deep vein thrombosis and pulmonary embolism, atrial fibrillation, stroke, heart failure and cardiomyopathy. Studies that examined CVD risk factors including hypertension and other subclinical outcomes or cardiovascular diseases that are not manifested via the stress pathway [20] such as congenital heart disease and rheumatic heart disease were excluded. As this review aimed to make a comparison between the CVD incidence between informal carers and non-carers, studies that did not include a non-caring comparator group in their analysis were also excluded.

Title and abstract screening was carried out independently by two reviewers: one reviewer (AL), and one other contributor (TK, YT, JE, or HMD), screened all records to determine if they were eligible for full-text review. Conflicts were resolved by consensus and unresolved disagreements were taken to a third reviewer. Full-text screening was conducted by two reviewers (AL & JE), and any conflicts were discussed until a consensus was reached.

Data extraction was performed by one reviewer (AL) utilising a data extraction form in Microsoft Excel. Data extraction captured key information from the nine studies eligible for inclusion, including author name, year of publication, study location, study design, sample population, exposure, outcome, data collection, statistical method, covariates, and study findings.

The ROBINS-E tool for assessing risk of bias in non-randomised studies was used to assess the quality of the included studies based on comparisons to an idealised target trial. ROBINS-E is designed to be used in systematic reviews, enabling users to make overall and specific judgements about the risk of bias (RoB) of the included studies across seven different domains [26].

RoB assessment (via ROBINS-E) first entailed making general considerations for all studies which included devising a minimal set of confounders determined by the reviewers as being most likely to produce bias in the associations observed. Secondly, the studies were individually described within the context of an ideal target trial. Lastly, one reviewer (AL) and one of three other reviewers (TK, YT, or JE) independently assessed the RoB for each study across the seven domains – confounding, selection of participants, classification of exposures, departure from intended exposure, missing data, measurement of outcomes, and selection of the reported result. Each domain was marked as

either low, moderate, serious, or critical, with the most severe judgement across all domains becoming the overall assessment for each study. Conflicts in RoB assessment were discussed until a consensus was reached with one constant reviewer (AL) ensuring that judgements were applied consistently.

3. Results

Study Characteristics A total of 3603 records were exported from the six databases and uploaded to Covidence, a web-based tool for conducting systematic reviews [27]. Before screening commenced, 1716 duplicate results were removed (1598 duplicates were identified automatically by Covidence, and 118 duplicates were manually removed by reviewers). The remaining 1888 records underwent title and abstract screening, with 34 studies deemed eligible for full-text review (See Appendix 2 for full list). Of these 34 studies, seven studies had no comparator group, seven measured the wrong outcome, four had no full-text available, four used a wrong study design, and three examined the wrong exposure. Following full-text screening, nine studies had been identified as eligible for inclusion in the systematic review. (see Table 1, Fig. 1)

Eight out of the nine studies included were longitudinal in design [28–35], with one cross-sectional study [36]. Five different studies used populations residing in the United States [28,31,32,35,36], with one study each based in Japan [33], Northern Ireland [34], Sweden [30], and London, UK [29]. Four of the studies explored the cardiovascular health of family caregivers [28,30,31,33] and the other five did not specify a particular relationship between carer and care recipient [29, 32,34–36]. Two of the studies stratified their results between males and females [28,30], with another study consisting only of female participants [32]. The six remaining studies all presented results that were not disaggregated by gender [29,31,33–36].

Two studies inferred the caregiving status of their participants based on a known relationship that participants had to an individual who had a specific disease, with one study exploring CVD incidence among spouses of cancer patients [30] and the other investigated CVD in household members of people with Alzheimer's disease [35]. All but one of the other seven studies had participants self-report their caregiving status, with the remaining study examining caregivers who were identified by the care-recipient [31].

Three of the studies which used self-reported caregiving as the exposure also recorded the weekly frequency of caregiving in hours [32–34]. Four studies used validated measures to assess the incidence of CVD outcomes [29,30,34,35], while one study only verified fatal CVD incidences, using self-report for non-fatal outcomes [32]. All other studies measured CVD outcomes by self-report [28,31,33,36].

Risk of Bias Assessment Across the nine included studies, the overall quality of the evidence assessing the association between informal caring and CVD incidence was judged to be at moderate to serious risk of bias (RoB). Four studies were deemed to be at moderate RoB overall [28, 31,33,34], whilst five studies were considered to be at serious RoB [29, 30,32,35,36]. Bias due to confounding was typically moderate or serious, with four studies each judged as moderate [28,29,31,33] and serious [30,32,35,36], whilst one study was considered low risk [34]. Studies that failed to adjust for the minimum set of confounders (age, sex/gender, ethnicity, and socioeconomic status) were considered to have serious RoB due to confounding.

Bias in selection of participants into studies was generally low (n = 5), with the remaining four studies considered to have moderate risk [32,33,35,36]. RoB in classification of exposures was moderate for all but three studies [30,35,36] which were deemed at serious risk. RoB due to departures from intended outcomes was more mixed, with two studies judged at low risk [31,36], four studies were considered at moderate risk [28,32–34], and three studies were rated as serious RoB [29,30,35]. Similarly, RoB due to missing data saw two studies at low risk [28,34], five studies with moderate risk [29,31–33,36], and two with serious risk [30,35] (see Table 2).

The RoB judgement for measurement of outcomes was split with four studies considered low [29,30,34,35] and five studies deemed moderate [28,31–33,36]. Overall, the RoB in selection of the reported result was considered the least severe RoB category, as seven studies were deemed to be at low risk [28,29,32–36] and the other two [30,36] were considered to be at moderate risk. An effect direction plot is displayed in Table 3., summarising particular attributes of each of the nine included studies and indicating whether each study observed either a positive association, negative association, or no association between providing care and CVD.

Qualitative Synthesis Of the two studies that inferred caregiving within the context of an existing relationship (rather than measuring reported caregiving), both observed increases in cardiovascular outcomes for caregivers [30,35]. Ji et al. [30] saw standardised incidence ratios for CHD or stroke hospitalisations increase among both male and female spouses of cancer patients after the date of their spouse's diagnosis, compared to before the diagnosis. Similarly, Suehs et al. [35] found increases in prevalence ratios of CVD outcomes (including ischaemic heart disease, peripheral vascular disease, and other forms of heart disease) among household members of people with Alzheimer's disease compared with individuals who were not household members of a person with Alzheimer's disease.

Four studies asked participants to self-report their caregiving status as a binary yes/no variable [28,29,31,36]; the associations between this exposure and cardiovascular outcomes were varied across these studies. The study by Burr et al. [28] observed no difference in the hazard ratio of heart attack, stroke, or CVD-related mortality for either men or women aged over 51 years providing informal care to a parent or spouse, compared to a non-caring comparator. Buyck et al. [29] also observed no difference in the hazard ratio of CHD amongst London-based office workers who provided informal care (compared to a non-caring control group), but did observe increases in the hazard ratio of CHD for carers who were aged over 50 years, married, or of low socioeconomic position. In contrast, Kim et al. [31] observed an increase in the odds of heart disease among long-term family caregivers of cancer patients, compared to participants who were providing care at baseline but had stopped caregiving at follow-up. Additionally, Kim et al. [31] found that family caregivers whose care recipient had died during follow-up had even larger odds of heart disease compared with former caregivers. Conversely, in the only cross-sectional study included in this review, Manley et al. [36] noted scarce difference in the prevalence of myocardial infarction, CHD, and stroke among United States army veterans who had provided informal care within the month prior to being surveyed, compared to veterans who did not provide care.

Three of the included studies asked participants to report their hourly caregiving intensity in a typical week (in addition to their caregiving status), acknowledging that the frequency of providing informal care may be as important as caregiving status [32–34]. The study by Lee et al. [32] found an increase in CHD risk for female registered nurses who provided at least 9 h of informal care per week to ill or disabled individuals, compared to those who provided no informal care. Likewise, the study by Miyawaki et al. [33] saw an increase in the risk of non-fatal CHD among family caregivers aged 50–59 years at baseline who provided more than 20 h of care per week, compared to non-carers. O'Reilly et al. [34] observed a reduction in the risk of CVD-related mortality for all informal carers (compared to non-carers) regardless of caring intensity.

4. Discussion

This systematic review investigated the association between unpaid informal care and cardiovascular disease incidence and found that there was no clear association between informal caregiving status and CVD incidence when caregiving was assessed as a binary variable. However, the evidence suggested that there was an association between more

Table 1
Descriptive summary of included studies.

First Author (Publication Year)	Location	Study Design	Analytical Sample	Exposure and Measurement	Cardiovascular Outcomes	Main Findings
Burr (2018)	United States	Longitudinal	11,418 (adults aged 51+ years)	*Spousal Caregiving* Self-reported helping a spouse with at least one Activity of Daily Living (ADL) limitation or Instrumental Activity of Daily Living (IADL) limitation *Parental Caregiving* Self-reported spending >100 h in the past 2 years helping parents get dressed, eat, or bathe and spending >100 h helping parents with household chores, errands, or transportation.	Self-reported non-fatal heart attack or stroke CVD-related death ascertained by proxy	No association observed for incident CVD in women who cared for their spouses or parents compared to women who provided no caregiving. HR = 0.85, 95% CI = [0.64, 1.13] No association observed for incident CVD in men who cared for their spouses or parents compared to men who provided no caregiving. HR = 1.22, 95% CI = [0.92, 1.63]
Buyck (2013)	London, UK	Longitudinal	7925 (London-based office workers)	*Caregiving Status* Self-reported yes/no answer to the question "Are you currently providing any personal care to an aged or disabled relative(s)?"	Coronary heart diseases including fatal CHD, non-fatal myocardial infarction, and angina. These were self-reported and then validated by the Hospital Episode Statistics database or by contacting GPs.	There was no clear overall association observed of incident CHD in caregivers compared to no caregivers. HR = 1.20, 95% CI = [0.98, 1.47] There was an observed increase in incident CHD for caregivers who were aged >50 years (HR = 1.28, 95% CI = [1.01, 1.63]), married or cohabiting (HR = 1.30, 95% CI = [1.04, 1.63]), or of low socioeconomic status (HR = 1.38, 95% CI = [1.07, 1.77]) compared to non-caregivers
Ji (2012)	Sweden	Longitudinal	1,352,656 (spousal pairs)	*Spousal Caregiving* Individuals who had children with and had lived for over 10 years with a person on the Swedish Cancer Registry were assumed to be spousal carers, they were identified using the Multi-Generation Registry	Hospitalisation due to CHD or stroke, including haemorrhagic stroke and ischaemic stroke, identified with the Swedish Hospital Discharge Register	At baseline (pre-cancer diagnosis), spouses of women with cancer had a slight increase in the standardised incidence ratio of CHD (SIR = 1.03, 95% CI = [1.01, 1.04]) and ischaemic stroke (SIR = 1.05, 95% CI = [1.02, 1.08]) compared to spouses of women without cancer. There was no baseline difference in haemorrhagic stroke risk (SIR = 1.04, 95% CI = [0.98, 1.11]. After women's cancer diagnosis, their spouse's had increased risk of CHD (SIR = 1.13, 95% CI = [1.10, 1.16]), ischaemic stroke (SIR = 1.24, 95% CI = [1.21, 1.27]), and haemorrhagic stroke (SIR = 1.25, 95% CI = [1.18, 1.32]) At baseline (pre-cancer diagnosis), spouses of men with cancer had reduced risk of CHD (SIR = 0.88, 95% CI = [0.86, 0.90]), ischaemic stroke (SIR = 0.86, 95% CI = [0.84, 0.89]), and haemorrhagic stroke (SIR = 0.81, 95% CI = [0.76, 0.87]) compared to spouses of men without cancer. After their spouse's diagnosis, these risks increased with CHD SIR = 1.13 (95% CI = [1.10, 1.16]), ischaemic stroke SIR = 1.29 (95% CI = [1.26, 1.32]), and haemorrhagic stroke SIR = 1.27 (95% CI = [1.19, 1.34])
Kim (2015)	United States	Longitudinal	1517	*Family Caregiving* Individuals nominated by cancer patient as primary family carer. Current caregiving status was self-reported at each follow-up.	Self-reportedly receiving a physician's care or taking prescription medication for heart-related diseases including angina, CHD, cardiac arrest, congestive heart failure, heart attack, heart murmur, irregular heartbeat, and pacemaker	In comparison to participants who were no longer providing care at the final follow-up, there was greater odds of heart disease for current carers, OR = 1.12 (95% CI = [1.03, 1.21]). For bereaved carers, these odds were even higher, OR = 1.66 (95% CI = [1.39, 1.98]).
Lee (2003)	United States	Longitudinal	54,412 (female	*Caregiving Status* Self-reported yes/no answer to	Self-reported non-fatal myocardial infarction was verified using	There was no difference in the relative risk of CHD for participants

(*continued on next page*)

Table 1 (*continued*)

First Author (Publication Year)	Location	Study Design	Analytical Sample	Exposure and Measurement	Cardiovascular Outcomes	Main Findings
			registered nurses)	the question "Outside of your employment, do you provide regular care to any of the following? Disabled or ill spouse, disabled or ill parent, and disabled or ill others" Categories of weekly hours spent caring were also reported for each type of care	individual's medical records Fatal CHD was reported by family members or postal authorities and verified by hospital records, autopsy, or death certificate	who performed <9 h of informal care per week compared to non-caregivers (RR = 1.11, 95% CI = [0.54, 2.25]). Caregivers providing ≥9 weekly hours of care had an increase in CHD risk (RR = 1.82, 95% CI = [1.08, 3.05])
Manley (2019)	United States	Cross-sectional	56,985 (US army veterans)	*Caregiving Status* Self-reported yes/no answer to the question "People may provide regular care or assistance to a friend or family member who has a health problem, long-term illness, or disability. During the past month did you provide any such care to a friend or family member?"	Self-reported presence or absence of myocardial infarction, coronary heart disease, or stroke	There was scant difference in the prevalence of MI (10.8% vs 10.6%), CHD (10.3% vs 10.3%), and stroke (5.5% vs 4.9%) for veteran carers vs non-caregiving veterans. Using these prevalence estimates and the size of the exposure and the comparator group, we derived odds ratios for each outcome. OR(MI) = 1.02, p = 0.67. OR(CHD) = 1.00, p = 0.98. OR(stroke) = 1.13, p = 0.18
Miyawaki (2017)	Japan	Longitudinal	25,121 (aged 50–59 years)	*Family Caregiving* Self-reported yes/no answer to the question "Are you currently caring for any relatives regardless of whether they are within or out of the household?" Categories of weekly hours spent caring were also reported as well as care recipient (parents, spouse's parents, or other)	Self-reported diagnosis of heart disease (myocardial infarction or angina pectoris), only non-fatal CHD was included	There was no overall difference in the risk of incident CHD for carers compared to non-carers. HR = 1.13, 95% CI = [0.92, 1.40]. For carers providing over 20 weekly hours of care there was an observed increase in incident CHD risk compared to non-carers. HR = 1.78, 95% CI = [1.23, 2.58]. For carers providing less than 20 h of care per week there was no difference in CHD incidence compared with non-carers.
O'Reilly (2015)	Northern Ireland	Longitudinal	1,122,779 (aged 25+ years)	*Caregiving Status* Self-reported yes/no answer to the question "Do you look after, or give any help or support to family members, friends, neighbours or others because of either: long-term physical or mental ill health/disability; problems related to old age?" Categories of weekly hours spent caring were also reported for each type of care	Cardiovascular-related mortality, ascertained using validated records	The risk of mortality due to any cardiovascular cause for any frequency of caregiving was reduced compared to that of non-carers. For carers providing 1–19 weekly hours of care, HR = 0.70, 95% CI = [0.62, 0.81]. For those providing 20–49 weekly hours of care, HR = 0.80, 95% CI = [0.66, 0.97]. For those providing 50 or more hours of care per week, HR = 0.75, 95% CI = [0.67, 0.84]
Suehs (2014)	United States	Longitudinal	1861 (cohabiting dyads)	Household members of people with Alzheimer's Disease were assumed to be carers	Ischaemic heart disease, peripheral vascular disease, diseases of pulmonary circulation, heart failure, cerebrovascular disease, venous thromboembolism, and other forms of heart disease based on pharmacy claims	There was increased prevalence of all cardiovascular outcomes for household members of individuals with Alzheimer's Disease compared to non-Alzheimer's Disease household members. The prevalence ratio of ischaemic heart disease = 1.16, p < 0.001; peripheral vascular disease = 1.16, p = 0.02; diseases of pulmonary circulation = 1.14, p = 0.21; heart failure = 1.12, p = 0.09; cerebrovascular disease = 1.11, p = 0.06; venous thromboembolism = 1.02, p = 0.88; other forms of heart disease = 1.13, p < 0.001

intense caregiving (providing >9 or >20 h of informal care per week) and CVD incidence. This was consistent with the 2012 study by Capistrant et al. [37] which observed an increase in CVD incidence among spousal caregivers who provided ≥14 h of care per week compared with less intense caregivers. Of the nine studies that contributed to this systematic review, four [29–31,33] were also included in the aforementioned 2021 systematic review by Ahn et al. [24] which examined CVD risk and incidence among family carers of adults with chronic conditions.

Providing more intense caregiving has been linked with increased stress [38] and studies observing an increase in CVD incidence among more intense caregivers add robustness to the path model hypothesised

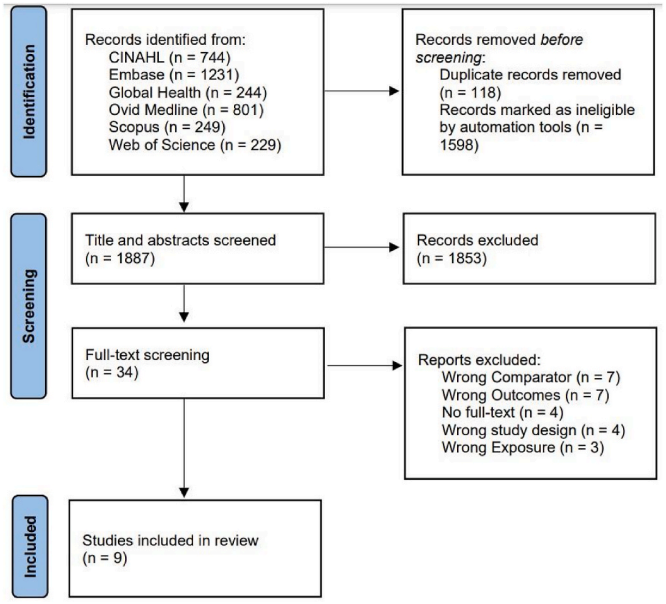


Fig. 1. Prisma Flow Diagram of study selection.

by Vitaliano et al. [20], linking chronic stress with CHD. Importantly, it appears that maintaining caregiving intensity over long periods could serve as a catalyst for the development of this pathway.

It is difficult to holistically assess the relationship between informal care and CVD, as different studies, both in this review and in the wider literature, have examined varying kinds of caregiving exposures (i.e., to care-recipients with a particular condition or within a specific caregiver-recipient relationship) as well as numerous cardiovascular outcomes. This heterogeneity between study designs was a considerable limitation of this review, particularly given the variance between studies in ascertaining participants' caregiver status, as well as whether or not intensity was recorded.

Similarly, the heterogeneity of the cardiovascular outcomes assessed across the nine studies make comparisons between them difficult. Four studies exclusively used self-reported measures of cardiovascular events, while others used medical records to verify the outcome. In addition, the studies by Burr et al. (2018), Buyck et al. (2013), and Lee et al. (2003) [28,29,32] all reported both fatal and non-fatal CVD outcomes as a single outcome. This may have produced bias in these results given that O'Reilly et al. [34] observed a reduction in CVD-related mortality for informal carers, consistent with other studies that associated caregiving with decreased mortality [18,19].

Ultimately, due to the significant heterogeneity observed between the nine included studies, a meta-analysis was not justified. As such, the potential impact of publication bias on these results was unable to be examined. Another limitation of this review is that information bias was likely to be present among the included studies, owing to the use of self-reported data to answer the research question. In the two studies that made an inference about caregiving exposure status based on participants' relationship to a person who was known to be ill [30,35], there is a risk of misclassification bias, as caregiving could not reliably be ascertained simply from the relationship used to allocate exposure status. In these studies, it is likely that misclassification occurred by assignment of non-carers to the caregiving group and vice-versa, likely biasing the results of these studies toward the null. In studies that used self-reported exposure status, biases may also have been present. Recall bias and/or social desirability bias could have led to misclassification in measuring caregiving status or reporting caring intensity in these studies. Accurately answering the research question was further limited due to the time-varying nature of caregiving status, with all but one of the longitudinal studies included [31] making the assumption that caregiving status was fixed throughout follow-up time and that participants were not moving between exposure groups over the study duration.

Selection bias may also have been present, with certain studies selecting only participants who were of a certain age or had a particular professional background, limiting the generalisability of these findings. Additionally, the healthy caregiver effect may impact some of these studies. Ill health can act as a barrier to becoming a caregiver and influence individuals' selection into studies and can also serve as a possible factor for attrition. Moreover, the unmeasured outcome status of participants lost to follow-up could produce bias in longitudinal studies that did not account for biases from attrition. Confounding may have also been a source of bias, with four studies failing to meet the minimal set of confounders imposed in this review.

There were also some strengths of this review in achieving its objectives. All of the included studies compared the incidence of CVD

Table 2
ROBINS-E risk of bias assessment of included studies.

Author's name (year)	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of exposures	Bias due to departures from intended exposures	Bias due to missing data	Bias in measure-ment of outcomes	Bias in selection of the reported result	Overall bias
Burr (2018)	Moderate	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Buyck (2013)	Moderate	Low	Moderate	Serious	Moderate	Low	Low	Serious
Ji (2012)	Serious	Low	Serious	Serious	Serious	Low	Moderate	Serious
Kim (2014)	Moderate	Low	Moderate	Low	Moderate	Moderate	Low	Moderate
Lee (2003)	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Serious
Manley (2019)	Serious	Moderate	Serious	Low	Moderate	Moderate	Moderate	Serious
Miyawaki (2017)	Moderate*	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
O'Reilly (2015)	Low	Low	Moderate	Moderate	Low	Low	Low	Moderate
Suehs (2014)	Serious	Moderate	Serious	Serious	Serious	Low	Low	Serious

*Miyawaki et al. (2017) did not adjust for ethnicity in their analysis but due to the ethnic homogeneity of the Japanese population studied, this would have contributed negligible bias.

Table 3
Effect direction plot of included studies.

Study	Study Design	Caregiving Exposure	Effect Measure	Outcome Definition	All (No stratification by sex)	Female	Male
Burr (2018)	Longitudinal	Binary	HR	Heart attack, stroke or CVD-related fatality		◄►	◄►
Miyawaki (2017)	Longitudinal	Categorical*	HR	Angina or myocardial infarction	▲		
O'Reilly (2015)	Longitudinal	Categorical*	HR	CVD-related mortality	▼		
Kim (2014)	Longitudinal	Binary	OR	Receiving treatment for heart disease	▲		
Manley (2019)	Cross-Sectional	Binary	Prevalence	Myocardial infarction, CHD or stroke	◄►		
Suehs (2014)	Longitudinal	Binary	PR	Ischaemic heart disease	◄►		
Buyck (2013)	Longitudinal	Binary	HR	Angina, myocardial infarction, and fatal CVD	◄►		
Ji (2012)	Longitudinal	Binary	IR	Hospitalisation due to CHD or stroke		▲	▲
Lee (2003)	Longitudinal	Categorical*	RR	Myocardial infarction or fatal CHD		▲	

outcomes with a non-caring comparator group, and eight out of the nine included studies had a longitudinal study design. These allowed the review to maximise its ability to make a causal inference in answering the research question. Another strength of the review was the use of the ROBINS-E risk of bias assessment tool, a structured assessment tool of non-randomised observational studies.

This review also identifies specific areas for future research to be focused towards. As demonstrated by the breadth of caregiving definitions amongst the studies included in this review, there is not a single accepted description of informal caregiving that is applied within the literature. A standardised conception of caregiving that has been universally endorsed by experts would allow researchers to conduct studies that utilise a generalisable population of caregivers and make better comparisons between studies. In addition, longitudinal studies within the caregiving literature would also benefit from following up on participants' caregiving status to account for the time-varying nature of providing care for others, and more accurately reflect the reality of the lives of informal carers.

Nuances in the relationship between providing informal care and CVD incidence have also been established, and further research is required to understand how this effect might be modified by different variables such as caring intensity, type of care assistance provided, duration of caregiving (short-term vs long-term), relationship between caregiver and care recipient, or the type of illness of the care recipient. Examining these factors with a standardised definition of caregiving and accounting for participants who might move between caregiving and non-caregiving groups would improve the ability of future studies to infer the causality of the association between caregiving and CVD incidence. Such evidence is needed to inform mitigation or support strategies for caregivers in need of assistance.

5. Conclusion

The findings of our review highlight the need for more research to be conducted to explore the relationship between unpaid caregiving and CVD in greater detail. Specifically, examining caregiving intensity as well as caregiving status and treating it as a variable that can change throughout the follow-up duration will better enable assessment of the causal effect of caregiving on CVD outcomes. By accounting for participants who move between periods of caregiving and non-caregiving, studies will be better able to assess the causal effect of caregiving on CVD outcomes. Distinguishing between fatal and non-fatal CVD outcomes may also serve to elucidate the nature of the relationship between CVD and informal care and help guide future directions for research.

This systematic review addresses a research gap in the literature by synthesising studies that compared the incidence of CVD outcomes among informal carers against a non-caring comparator group. The findings of this review indicate that the association between providing informal care and the incidence of CVD is not clear, however, there is some evidence that CVD incidence is associated with more intense forms of informal caregiving.

Author's contributions

The study was conceived by TK, YT, and JE. All authors contributed to formulating the study design and literature search. Screening of studies was conducted by the authors and an additional contributor, HMD. AL wrote the manuscript and produced the figures and tables. All authors contributed to drafts of the manuscript and gave approval before submission.

No new data were generated or analysed in support of this research.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 1. Detailed Search Strategy 31st March 2022 (and alerts set for all databases)

CINAHL Complete (EBSCO)

("informal unpaid car*" OR "informal car*" OR "unpaid car*" OR "family car*" OR carer OR caregiv* OR "unpaid childcar*") AND (CVD* OR CHD* OR "cardiovascular disease*" OR "vascular disease*" OR "heart disease*" OR "arterial disease*" OR "coronary disease*" OR "coronary heart disease*" OR "cardiac disease*" OR "coronary artery disease*" OR "cardiovascular outcome*" OR "cardiovascular health") NOT ("congenital heart disease*" OR "rheumatic heart disease*") **744 Results**.

Embase Classic + Embase (OVID) *1947–2022 Week 12*

1. ("informal unpaid car*" or "informal car*" or "unpaid car*" or "family car*" or carer* or caregivers or "care givers").ab,kf,ti.
2. (CVD* or CHD* or "cardiovascular disease*" or "vascular disease*" or "heart disease*" or "arterial disease*" or "coronary disease*" or "coronary heart disease*" or "cardiac disease*").ab,kf,ti.
3. ("congenital heart disease*" or "rheumatic heart disease*").ab,kf,ti.
4. (1 and 2) not 3 **1231 Results**

Global Health (CAB)

("informal unpaid car*" OR "informal car*" OR "unpaid car*" OR "family car*" OR carer OR caregiv* OR "unpaid childcar*") AND (CVD* OR CHD* OR "cardiovascular disease*" OR "vascular disease*" OR "heart disease*" OR "arterial disease*" OR "coronary disease*" OR "coronary heart disease*" OR "cardiac disease*" OR "coronary artery disease*" OR "cardiovascular outcome*" OR "cardiovascular health") NOT ("congenital heart disease*" OR "rheumatic heart disease*") **244 Results**.

Ovid MEDLINE(R) ALL *1946 to March 29, 2022*

1. ("informal unpaid car*" or "informal car*" or "unpaid car*" or "family car*" or carer* or caregivers or "care givers").ab,kf,ti.
2. (CVD* or CHD* or "cardiovascular disease*" or "vascular disease*" or "heart disease*" or "arterial disease*" or "coronary disease*" or "coronary heart disease*" or "cardiac disease*" or "coronary artery disease*" or "cardiovascular outcome*" or "cardiovascular health").ab,kf,ti.
3. ("congenital heart disease*" or "rheumatic heart disease*").ab,kf,ti.
4. (1 and 2) not **3801 Results**

Scopus

((TITLE-ABS-KEY (("informal unpaid car*" OR "informal car*" OR "unpaid car*" OR "family car*" OR carer OR caregiv* OR "unpaid childcar*") W/10 (cvd* OR chd* OR "cardiovascular disease*" OR "vascular disease*" OR "heart disease*" OR "arterial disease*" OR "coronary disease*" OR "coronary heart disease*" OR "cardiac disease*" OR "coronary artery disease*" OR "cardiovascular outcome*" OR "cardiovascular health")) AND NOT TITLE-ABS-KEY (("congenital heart disease*" OR "rheumatic heart disease*")))) **249 Results**.

Web of Science

(TS=(("informal unpaid car*" OR "informal car*" OR "unpaid car*" OR "family car*" OR carer OR caregiv* OR "unpaid childcar*") NEAR/10 (CVD* OR CHD* OR "cardiovascular disease*" OR "vascular disease*" OR "heart disease*" OR "arterial disease*" OR "coronary disease*" OR "coronary heart disease*" OR "cardiac disease*" OR "coronary artery disease*" OR "cardiovascular outcome*" OR "cardiovascular health"))) NOT TS=("congenital heart disease*" OR "rheumatic heart disease*") **229 Results**

Appendix 2

Articles excluded after full-text review with reasons for exclusion.

	Article	Reason
1	Aggarwal, B., & Mosca, L. (2009). Heart Disease Risk for Female Cardiac Caregivers. *The female patient*, *34*(2), 42–45.	Wrong study design
2	Butts, B. et al. (2014). Caregiver Stress and Cardiovascular Disease Risk Among Female Family Caregivers of Persons With Heart Failure. *Journal of Cardiovascular Nursing*, *29*(5), 390–391.	No full text
3	Cannon, S., & Fawcett, J. (2018). Correlates of Psychological and Physical Health Outcomes among African American Caregiving Daughters. ABNF Journal, 29(3), 86–97.	Wrong outcomes
4	Capistrant, B.D., Moon, J.R. and Glymour, M.M. (2012) 'Spousal caregiving and incident hypertension', *American Journal of Hypertension*, 25(4), pp. 437–443.	Wrong outcomes
5	Capistrant, B.D. et al. (2012) 'Current and long-term spousal caregiving and onset of cardiovascular disease', *J Epidemiol Community Health*, 66(10), pp. 951–956.	Wrong comparator
6	Dorn, T. et al. (2007) 'Physical and mental health problems in parents of adolescents with burns — a controlled, longitudinal study', *Journal of Psychosomatic Research*, 63(4), pp. 381–389.	Wrong exposure
7	Drummond, M, Johnston, B, Quinn, TJ. Cutting through the intersections to care for caregivers: Secondary data analysis of a carers support service in Glasgow, Scotland. *Health Soc Care Community*. 2022; 30: 1334–1343.	Wrong comparator
8	Fleisher, J.E. et al. (2021) 'Chronic Comorbidities of Caregivers of Homebound Individuals with Advanced Parkinson's Disease (2209)', *Neurology*, 96(15 Supplement), p. 2209.	Wrong study design
9	Haley, W.E. et al. (2010) 'Caregiving Strain and Estimated Risk for Stroke and Coronary Heart Disease Among Spouse Caregivers', *Stroke*, 41(2), pp. 331–336.	Wrong outcomes

(*continued on next page*)

(*continued*)

10	Lakkur, S. et al. (2016) 'Abstract MP102: Family Caregiving is Associated with Increased Stroke Risk Among Strained Spouse Caregivers', *Circulation*, 133 (suppl_1), pp. AMP102–AMP102.	No full text
11	LaVela, S.L. et al. (2015) 'Factors related to caregiving for individuals with spinal cord injury compared to caregiving for individuals with other neurologic conditions', *The Journal of Spinal Cord Medicine*, 38(4), pp. 505–514.	Wrong comparator
12	Leggett AN, Sonnega AJ, Lohman MC. Till Death Do Us Part: Intersecting Health and Spousal Dementia Caregiving on Caregiver Mortality. Journal of Aging and Health. 2020; 32(7–8):871–879.	Wrong outcomes
13	Lin, C.-Y. et al. (2021) 'Abstract 13,305: The Relationship of Health Activation to Risk of Future Cardiovascular Disease Among Family Caregivers of Patients With Chronic Illness in Rural Dwellers', *Circulation*, 144(Suppl_1), pp. A13305–A13305.	Wrong outcomes
14	Mannion E. Alzheimer's disease: the psychological and physical effects of the caregiver's role. Part 1. Nurs Older People. 2008 May; 20(4):27–32.	Wrong study design
15	Möllerberg, M.-L. et al. (2016) 'The effects of a cancer diagnosis on the health of a patient's partner: a population-based registry study of cancer in Sweden', *European Journal of Cancer Care*, 25(5), pp. 744–752.	Wrong comparator
16	Mortensen, J. et al. (2018) 'Weekly hours of informal caregiving and paid work, and the risk of cardiovascular disease', *European Journal of Public Health*, 28(4), pp. 743–747.	Wrong comparator
17	Sanford JT, Johnson AD and Townsend-Rocchiccioli J (2005) 'The health status of rural caregivers', Journal of Gerontological Nursing, 31(4), pp. 25–54.	Wrong comparator
18	Savela, Roosa-Maria; Nykänen, Irma; Schwab, Ursula; Välimäki, Tarja Social and Environmental Determinants of Health Among Family Caregivers of Older Adults, Nursing Research: 1/2 2022-vol 71 - Issue 1 - p 3-11	Wrong exposure
19	Schulz, R. et al. (1997) 'Health effects of caregiving: The caregiver health effects study: An ancillary study of the cardiovascular health study1', *Annals of Behavioral Medicine*, 19(2), pp. 110–116.	Wrong outcomes
20	Schulz, R. et al. (2009) 'Spousal Suffering and Partner's Depression and Cardiovascular Disease: The Cardiovascular Health Study', *The American Journal of Geriatric Psychiatry*, 17(3), pp. 246–254.	Wrong comparator
21	Shaffer, K. M. et al. (2013). Cardiovascular diseases in cancer caregivers: Effects of stress and depression. *Psychosomatic Medicine*, *75*(3), A-115	Wrong exposure
22	Shaffer, K. M. et al. (2013). Cardiovascular disease prevalence in cancer caregivers. *Annals of Behavioral Medicine*, *45*, S-106	No full text
23	Smith, J.L. et al. (2019) 'Abstract 14,709: Profile of Informal Rural Caregivers of Patients With Chronic Illnesses: At High Risk for Cardiovascular Disease', *Circulation*, 140(Suppl_1), pp. A14709–A14709.	No full text
24	Smith, JL, Chung, ML, Miller, JL et al. Profile of informal rural Appalachian caregivers of patients with chronic illnesses. *Journal of Rural Health*. 2022; 38: 240–250.	Wrong study design
25	Wu, K. K. et al. (2017). Impaired cardiovagal baroreflex in chronically stressed elderly caregivers. *Journal of the American Geriatrics Society*, *65*(S1), S-224	Wrong outcomes

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