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Title Page

Title: Association between osteoarthritis and cardiovascular disease: systematic review and meta-analysis.

Running Title: Osteoarthritis and cardiovascular disease: systematic review

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No author has any conflicts of interest in relation to this paper.

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Keywords: osteoarthritis; cardiovascular disease; cerebrovascular disease; myocardial infarction; hypertension.

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Abstract

Background: To examine for a possible relationship between osteoarthritis and cardiovascular disease (CVD).

Design: A systematic review and meta-analysis

Methods: Published and unpublished literature from: MEDLINE, EMBASE, CINAHL, the Cochrane Library, OpenGrey and clinical trial registers. Search to 22nd November 2014. Cohort, case-control, randomised and non-randomised controlled trial papers reporting the prevalence of CVD in osteoarthritis were included.

Results: Fifteen studies with 32,278,744 individuals were eligible. Pooled prevalence for overall CVD pathology in people with osteoarthritis was 38.4% (95% Confidence interval (CI): 37.2% to 39.6%). Individuals with osteoarthritis were almost three times as likely to have heart failure (Relative Risk (RR): 2.80; 95% CI: 2.25 to 3.49) or ischaemic heart disease (RR: 1.78; 95% CI: 1.18 to 2.69) compared to matched non-osteoarthritis cohorts. No significant difference was detected between the two groups for the risk of experiencing myocardial infarction or stroke. There was a three-fold decrease in the risk of experiencing a transient ischaemic attack in the osteoarthritis cohort compared to the non-osteoarthritis group.

Conclusions: Prevalence of CVD in patients with OA is significant. There was an observed increased risk of incident heart failure and ischaemic heart disease in people with OA compared to matched controls. However the relationship between OA and CVD is not straight-forward and there is a need to better understand the potential common pathways linking pathophysiological mechanisms.

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Keywords: osteoarthritis; cardiovascular disease; cerebrovascular disease; myocardial infarct; hypertension

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Introduction

Osteoarthritis (OA) is a common musculoskeletal disorder that presents with joint pain and stiffness, fatigue and consequently reduces people's function and quality of life.[1,2] Osteoarthritis of the knee has a prevalence of over 250 million people globally.[3] It is anticipated that this number will rise sharply in the future due to rapidly growing, ageing populations paralleled with the increasing prevalence of obesity. As a result, osteoarthritis is expected to impose a significant burden to the health economy. This will have a particular major burden on primary care, where it is predicted that by 2032 an additional 26,000 per one million patients aged over 45 years will consult their general practitioner with osteoarthritis compared to 2012.[4]

Cardiovascular diseases (CVD) such as stroke and myocardial infarction (MI) are a leading cause of mortality, accounting for 17.3 million people globally, and expected to rise to 23.3 million by 2030.[5] Previous studies have reported an association between chronic musculoskeletal diseases and CVD such as MI, cerebrovascular disease, peripheral vascular disease and heart failure.[6-8] Most notably, such an association has been reported for rheumatoid arthritis,[9] fibromyalgia[10] and low back pain.[11] Traditional risk factors for CVD, including age, male sex, obesity, family history, smoking and diabetes mellitus,[12] are also associated with the development and progression of symptomatic osteoarthritis,[13,14] potentially highlighting shared pathophysiological processes/pathways in their development.

It has been hypothesised that genetic, metabolic and neuroendocrine factors may also increase the prevalence of osteoarthritis.[15] Principally this may be associated with excessive proinflammatory cytokine production associated with osteoarthritis and with atherogenic effects associated with hypertension. The former has also been associated with the microvasculature of subchondral bone, which plays a role in the pathogenesis of osteoarthritis.[16,17] Many of these inflammatory processes and cytokines contribute to vascular

inflammation and atherosclerosis development that underlie many CVD such as hypertension, MI, heart failure and cerebrovascular disease.[18] The interrelationship between osteoarthritis and CVD, their shared risk factors and underlying pathophysiological mechanisms are complex and it is unknown whether patients with osteoarthritis are at increased risk of CVD, independent of their risk factor profile and age.

Therefore the purpose of this study is to systematically examine the literature to determine whether there is an association between osteoarthritis and CVD, such as cardiac failure, MI, stroke and peripheral vascular disease, and to quantify such associations using meta-analysis techniques where feasible.

Materials and Methods

The systematic review was conducted in accordance with the PRISMA guidelines[19] and followed a published predetermined protocol (PROSPERO CRD 42014007021).

Data Sources and Searches

Two reviewers (AJH and BS) independently conducted the searches of electronic databases including: MEDLINE, EMBASE, CINAHL, AMED (via Ovid), BNI, PsycINFO, Cochrane Library, PubMed and the PEDro database from their inception to 22nd November 2014. An example of the MEDLINE search strategy is presented in **Supplementary Table 1**. The search terms were modified for individual databases.

Unpublished and trial registry databases were screened and included: OpenGrey, the WHO International Clinical Trials Registry Platform, Current Controlled Trials and the UK National Research Register Archive from their inception to 22nd November 2014. All references lists of all potentially eligible studies and review papers were searched to identify any studies initially omitted.

Study Selection

Studies were included if they were conducted in humans and were case-controlled cohort or cross-sectional studies investigating the association between osteoarthritis and CVD, and which recorded osteoarthritis according to recognised criteria (e.g. American College of Rheumatology definitions[20]), self-report or self-reported physician-diagnosed osteoarthritis. We considered participants with osteoarthritis affecting any joint. Studies which recruited people with non-osteoarthritis diagnoses such as rheumatoid arthritis, fibromyalgia or chronic pain were

excluded, unless data for osteoarthritis were presented in an extractable form. Studies were included if there was a report of a CVD event (e.g. MI, ischaemic heart disease (defined as coronary artery disease or stable angina), stroke, peripheral vascular disease, atherosclerosis, chronic cardiac failure). Cardiovascular disease was defined as a composite end-point of a diagnosis of stroke, MI, heart failure, coronary heart disease, peripheral vascular disease or atherosclerosis. We were interested in any CVD events and not just first-time cardiovascular events. We also included the baseline data of any randomised controlled trials reporting the relationship between CVD and osteoarthritis. Single-case study papers were excluded. No restrictions were placed on the age or language of publication.

Based on the eligibility criteria, two reviewers (AJH and BS) independently reviewed the titles and abstracts from potentially relevant papers identified through the aforementioned search strategy. The full-text of all potentially eligible papers was reviewed before making a final decision on eligibility. Any disagreements in paper eligibility were resolved through a senior reviewer (TS).

Data Extraction and Quality Assessment

Data were extracted onto a data extraction form by one reviewer (AJH) and verified by two further reviewers (BS and TS). Data extracted included: country in which the study was conducted; joint affected by osteoarthritis; number of cases and controls; gender of participants; mean age of cases and controls; reported co-morbidities; cardiovascular risk factors; method of assessing CVD presence or risk; prevalence of CVD in cases and controls (including adjustments in the model for case-control longitudinal studies); and type of CVD reported within cohorts.

Each included paper was critically appraised using the Critical Appraisal Skills Programme (CASP) 'Case Control' appraisal tool.[21] Each included paper was assessed for quality and bias by

one reviewer (AJH) and independently verified by a second reviewer (BS). Any disagreements in appraisal outcomes were discussed and resolved by a third reviewer (TS).

Data Synthesis and Analysis

Where clinical and statistical homogeneity was apparent, we assessed the relationship between osteoarthritis and CVD using meta-analysis techniques. Thus the primary analysis was to assess the point prevalence of any CVD events. *A priori* conditions were defined as including (but not limited to): MI, stroke, transient ischaemic attack (TIA), peripheral vascular disease, atherosclerosis or chronic cardiac failure in people with osteoarthritis. Secondly, we assessed the relative risk (RR) and 95% confidence intervals (CI) of incident of CVD (as defined above) in participants with osteoarthritis compared to participants with non-osteoarthritis in cohort studies. Where possible, data analyses were adjusted for variables such as age, gender, smoking habit, alcohol consumption, body mass index (BMI) as possible CVD risk factors. Study statistical heterogeneity was assessed using the I-squared test.

Subgroup analyses were planned to assess whether there was a difference in prevalence or relative risk of CVD events dependent on anatomical region affected by osteoarthritis. It was not possible to undertake a subgroup analysis by region of osteoarthritis due to the current data available.

Analyses were performed using STATA version 12.0 (StataCorp LP, Texas, USA) and Revman Version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Role of Funding Sources

No funding was received for the conduct of this systematic review.

Results

Search strategy results

A total of 1624 citations were identified from the search strategy. After reviewing the titles and abstracts, 15 were eligible based on our *a priori* eligibility criteria. A summary of the search results is presented in **Figure 1**.

Critical appraisal

The results of the critical appraisal are presented in **Supplementary Table 2**. Overall, the evidence-base presented was of high methodological quality. A recurrent strength across the evidence-base were that the exposure to osteoarthritis and outcomes of CVD appeared to be measured and assessed in a robust manner in all studies except Jonsson et al[22] study which did not report how CVD status was assessed. All studies with the exception of Reid et al[23] accounted for important confounding variables such as age, gender, co-morbidities and lifestyle risk factors for CVD such as smoking, alcohol consumption and BMI in their analyses. The principle limitation with regards to quality of studies was an inadequate follow-up duration as four out of 15 studies were cross-sectional.[24-27]

Characteristics of included studies

A summary of the included studies characteristics is presented in **Supplementary Table 3**. This included six cross-sectional study.[23,28-32] four prospective longitudinal cohort studies,[22,24,25,33] three case-control studies[17,26,34,35] and one retrospective cohort study.[27] A total of 32,278,744 participants from the 15 studies (11,027,587 males; 20,763,074 females) were included. A total of 254,440 events of CVD within cases and 417,779 events in controls were reported from the 10 studies which presented this data. The mean age across the studies for osteoarthritis cases ranged from 58.2 years to 68.5 years, whilst the control groups were marginally younger with a mean ranging from 51.0[29] to 67.2 years.[32] The assessment of CVD was performed by various

approaches including medical history and examination, laboratory and clinical assessments and self-reporting (**Supplementary Table 3**). The documented CVD risk factors are presented in **Supplementary Table 4**.

Primary analysis: Prevalence of CVD

The findings on prevalence of CVD for people with osteoarthritis are presented in **Table 1**. There was a high prevalence when CVD was considered for all CVD pathologies with a pooled prevalence of 38.4% (95% CI: 37.2% to 39.6%) in osteoarthritis cases compared to controls which was 9% (95% CI: 8% to 9%; p=0.01). However, the prevalence for specific CVDs was low, ranging from 9% (95% CI: 8% to 10%) for ischaemic heart disease in the osteoarthritis compared to 4% (95% CI: 4% to 4%) in the control group (p=0.006) and 2% (2% to 3%) in the osteoarthritis participants for TIAs compared to 6% (95% CI: 6% to 6%) in the control group (p<0.001). However, as **Table 1** indicates, the prevalence for CVD as a whole was significantly greater in the osteoarthritis cohort (prevalence: 38% versus 9%) compared to the controls (p=0.01).

Secondary analysis: Comparative relative risk of CVD in osteoarthritis and non-osteoarthritis cohorts?

A summary of the comparison between the relative risk of CVD between osteoarthritis and non-osteoarthritis cohorts is presented in **Figure 2**. There were statistically significant increased relative risks (over two fold) of heart failure and ischaemic heart disease in participants with osteoarthritis compared to non- osteoarthritis participants (**Table 1**). The relative risk and corresponding 95% CI of these conditions were 2.80 (95% CI: 2.25 to 3.49) and 1.78 (95% CI: 1.18 to 2.69) respectively. Interestingly, the risk of TIA was lower in the osteoarthritis cohort compared to the non-osteoarthritis cohort; people with osteoarthritis had a three-fold decreased risk of experiencing a TIA compared to the non-osteoarthritis group (RR: 0.33; 95%

CI: 0.27 to 0.41). There was no statistically significant difference in risks of experiencing a MI or stroke between the osteoarthritis and non-osteoarthritis cohorts ($p \geq 0.09$; **Table 2**).

Discussion

To our knowledge, this is the first and the largest systematic review and meta-analysis involving data from over 32 million participants to investigate the relationship between osteoarthritis and CVD both in terms of prevalence and risk of subsequent CVD. We established that people with osteoarthritis have significantly higher prevalence of overall CVD. Moreover, we found that individuals with osteoarthritis were over twice as likely to experience heart failure or ischaemic heart disease compared to people without osteoarthritis. Given the ageing global demographic and the fact that both conditions are prevalent in older age, it is more important than ever to consider these two groups of pathologies together.

Our findings of high prevalent levels of CVD among people with osteoarthritis are concerning for several reasons. First, CVD is a leading cause of premature mortality, with the World Health Organisation stating that it accounts for approximately half of all premature deaths across Europe.[5] In addition, osteoarthritis remains one of the most burdensome chronic musculoskeletal conditions affecting large numbers of people and is a leading cause of years lived with disability.[36]

Previous authors have suggested a potential synergistic effect between certain co-morbidities in the elderly.[37-39] Such hypotheses have included damage to blood vessels supplying the subchondral bone may contribute to the pathophysiology of osteoarthritis. Such could occur from hypertension which can result in vascular damage. Alternatively atherosclerosis and osteoarthritis are both being inflammatory processes involving inflammatory mediators which has demonstrated histological evidence of inflammation in vessel walls, joints and synovium.[18] However it remains unclear as to whether there is an interaction between osteoarthritis and CVD. There is also uncertainty as to how these may change and associate over time, and whether an ageing sample present with different co-occurring diseases over time. Further

longitudinal cohort studies will better inform how this occurs and whether there is a causal relationship between pathologies over a sufficient study period.

Interestingly, there were no statistically significant differences in risk of developing stroke and experiencing a MI, and even a protective effect with reduced risk of TIA observed in osteoarthritis cohorts. We observed high I^2 values indicating an extremely statistically heterogeneous nature of included studies for stroke and MI outcomes and this could potentially explain the null finding. This apparent discrepancy may arise with healthy survival bias as population characteristics (**Supplementary Table 3**) and CVD risk factors (**Supplementary Table 4**) from the included studies would support this hypothesis. This may therefore occur through the timing of these CVD events which occur later in life compared to hypertension and ischaemic heart disease, key risk factors for stroke and MI, respectively, which occur earlier in life. Treating these risk factors (hypertension and ischaemic heart disease) earlier in the life-course in people with osteoarthritis may attenuate their later CVD risk significantly in some of the cohorts included in the meta-analysis. One other plausible explanation which could account for the reduced risk of TIA is healthy survival bias, i.e. people with high CVD risk factors may had died prematurely and hence the studies which examined the risk of stroke, TIA and MI may consist of relatively healthier surviving osteoarthritis participants, whilst controls within these studies might have unknown CVD risk factors or pre-clinical stage which were not treated.

Our results have important clinical implications and considerations. It is important to note that an increased prevalence of CVD in osteoarthritis may impact on management options and outcomes for patients. Patients with comorbid diseases are less likely to be suitable candidates for surgical intervention, limiting the options available to treat and prevent progression of osteoarthritis. Furthermore those patients who do undergo surgery will be at an increased risk of peri- and post-operative complications e.g. anaesthetic complications, venous thromboembolism, MI and infection. Another important factor to consider in the association between osteoarthritis and CVD is the use of non-steroidal anti-inflammatories (NSAIDs), which

are known to result in increased risk of heart failure, hypercholesterolaemia, hypertension, heart disease and stroke.[40] This may precipitate CVD in patients treated for osteoarthritis, and may limit management options in patients with osteoarthritis who already have known CVD.

Outside of this, the cornerstone of the prevention and management of CVD is the promotion of physical activity.[41] People with osteoarthritis experience a range of barriers to engaging in physical activity, including higher levels of pain, increased BMI and lower levels of function.[42] Physiotherapists and other qualified professionals should seek to address and overcome these barriers to help the individual engage in physical activity. This may be particularly important given that physical activity demonstrates comparable effectiveness to pharmacological interventions in preventing cardiovascular disease outcomes,[43] and it is effective in reducing pain and disability in this group.[44] Therefore physical activity should be given a higher priority in the management of osteoarthritis throughout the duration of the condition to not only manage osteoarthritis symptoms but also to maintain cardiovascular health.

It was not possible, from this dataset, to determine a causal relationship between osteoarthritis and CVD pathologies as the compilation of evidence in this systematic review and meta-analysis were derived mainly from observational studies. This should be considered when interpreting the findings from this analysis. Moreover, it was not possible to conduct moderation analyses to consider factors that may account for this increased risk. Thus, the reasons why people with osteoarthritis appear more likely to experience high and increased levels of CVD is unclear but warrants attention.

The typical age of assessment varied e.g. ischaemic heart disease are more likely to occur in individuals over than 50 years of age whilst stroke and TIA are more prevalent after 65 years. Both may introduce selection bias by virtue of timing of event and hence people may receive preventative measures, or by selection bias due to people with less significant CVD events surviving and hence having a reduced risk of events (e.g. stroke) later events in life. It may also

be important to consider that this meta-analysis does not provide insight relating to the management of patients' cardiovascular risk factors or incident cardiovascular events and whether there is significant heterogeneity amongst patients with and without osteoarthritis. It is unclear whether patients with significant osteoarthritis receive similar access to evidence-based therapies and invasive interventions when diagnosed with CVD such as MI or stroke compared to patients without osteoarthritis, or whether patients with osteoarthritis are at a disadvantage for the provision of such therapy because of perceived frailty, risk or poor efficacy of therapies in such patients groups.

Our analysis suggests patients with osteoarthritis have a significantly higher prevalence of CVD than those without osteoarthritis and are twice as likely to develop ischaemic heart disease and heart failure. The optimal screening strategy for such patients with osteoarthritis is unclear with no clear recommendations in national society guidelines specifically for this patient group. Given the adverse risk factor profile in people with osteoarthritis that we report, we would advocate that future cardiovascular risk in these high-risk patients should be assessed formally using established cardiovascular risk scores such as SCORE, currently recommended for risk assessment in the asymptomatic adult without evidence of CVD by the European Society of Cardiology guidelines on CVD prevention (2012).[45] In people with osteoarthritis identified as low risk, risk assessment should be repeated at 5-year intervals in line with current recommendations if there are no significant changes in the major risk factor profile.[45] Aggressive risk factor management for those people with osteoarthritis found to be a high risk from future cardiovascular events should be advocated in addition to lifestyle changes. Such approaches in risk factor management have been shown to be effective, with up to 50% decreases in coronary heart disease mortality brought on by lifestyle changes and risk factors modifications.[46]

Study Limitations

Although this study is the first of its kind, our study has some limitations which are worth highlighting. First, four studies were cross-sectional and therefore directionality of the variables cannot be deduced with certainty. Second, the longitudinal studies had relatively short follow-up periods. Third, a large proportion of studies relied upon the medical and/or prescription records to ascertain CVD status. Studies relying upon this method are likely to be an under-estimate since some cardiovascular risk factors. Fourth, due to nature of the studies, we were unable to determine whether patients with osteoarthritis have worse CVD outcomes because of: a more adverse CVD risk factor profile; the use of anti-platelet, NSAID, statin or ACE-inhibitor medications which are known to influence CVD event rates; or more adverse outcomes independent of their risk profile which may point towards a shared pathophysiological mechanism. Finally, it was not possible to analyse the association between risk score and cardiovascular events occurrence, or to evacuate if people with a high risk (metabolic syndrome or diabetes for example) and osteoarthritis had a higher risk of CVD events compared with people at low risk. This data was not available from the current evidence-base, and may be best analysed through Individual Patient Data analyses. If such comparisons are possible with future data, we could better understand if osteoarthritis is associated with an increased risk with or without increasing risk factors.

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Table and Figure Legends

Figure 1: PRISMA Flow-Chart

Figure 2: Forest-plot presenting the relative risk of different CVD for OA and non-OA cohorts.

Table 1: Point prevalence of various markers of CVD in people with osteoarthritis

Table 2: Relative risk of CVD occurring compared to non-osteoarthritis control cohorts

Supplementary Table 1: Search terms adopted for the MEDLINE search strategy

Supplementary Table 2: Summary of critical appraisal assessment

Supplementary Table 3: Characteristics of included studies

Supplementary Table 4: Cardiovascular disease risk factors and assessment of CVD in the included studies.

Figure 1: PRISMA Flow-Chart

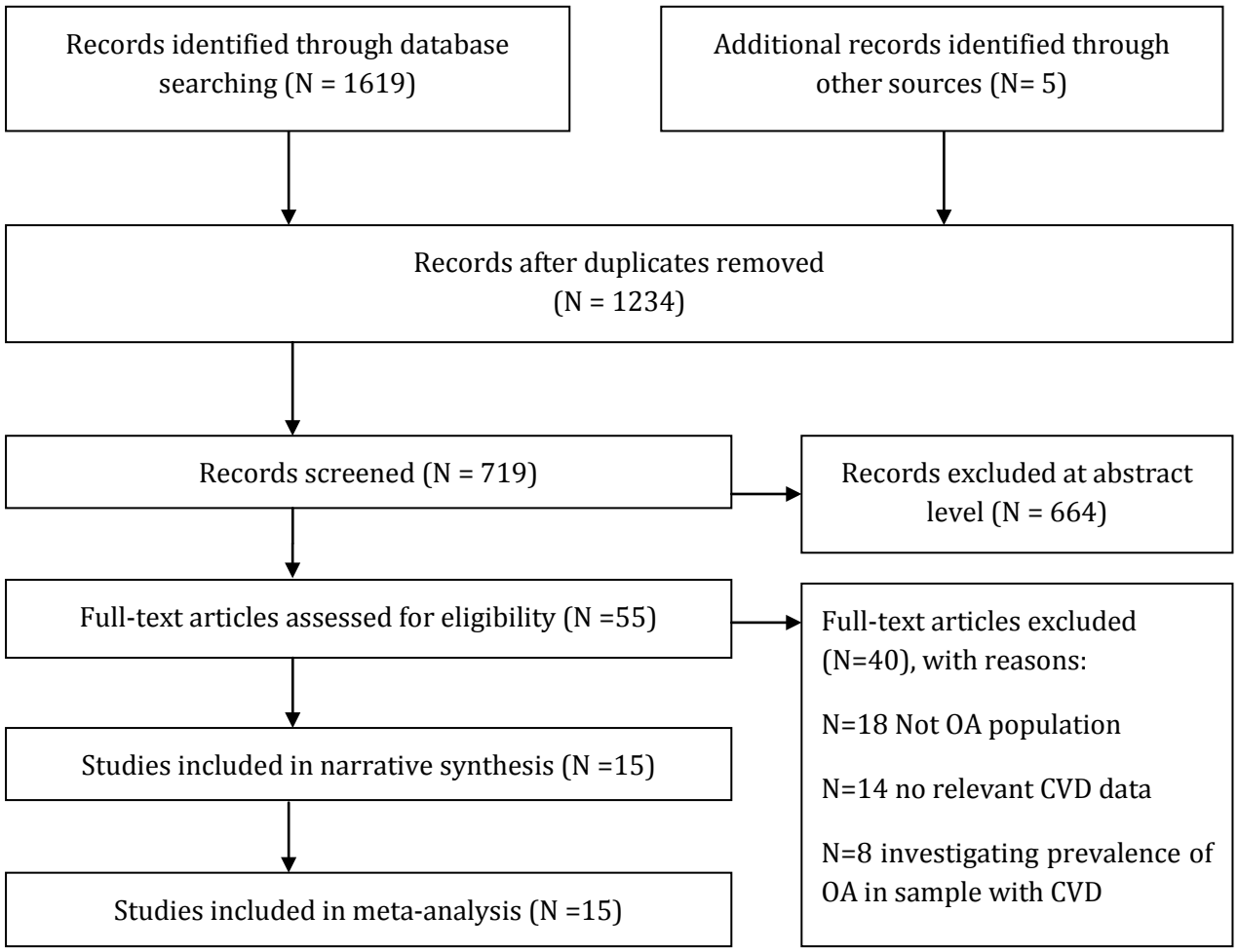

Figure 2: Forest-plot presenting the relative risk of different CVD for OA and non-OA cohorts.

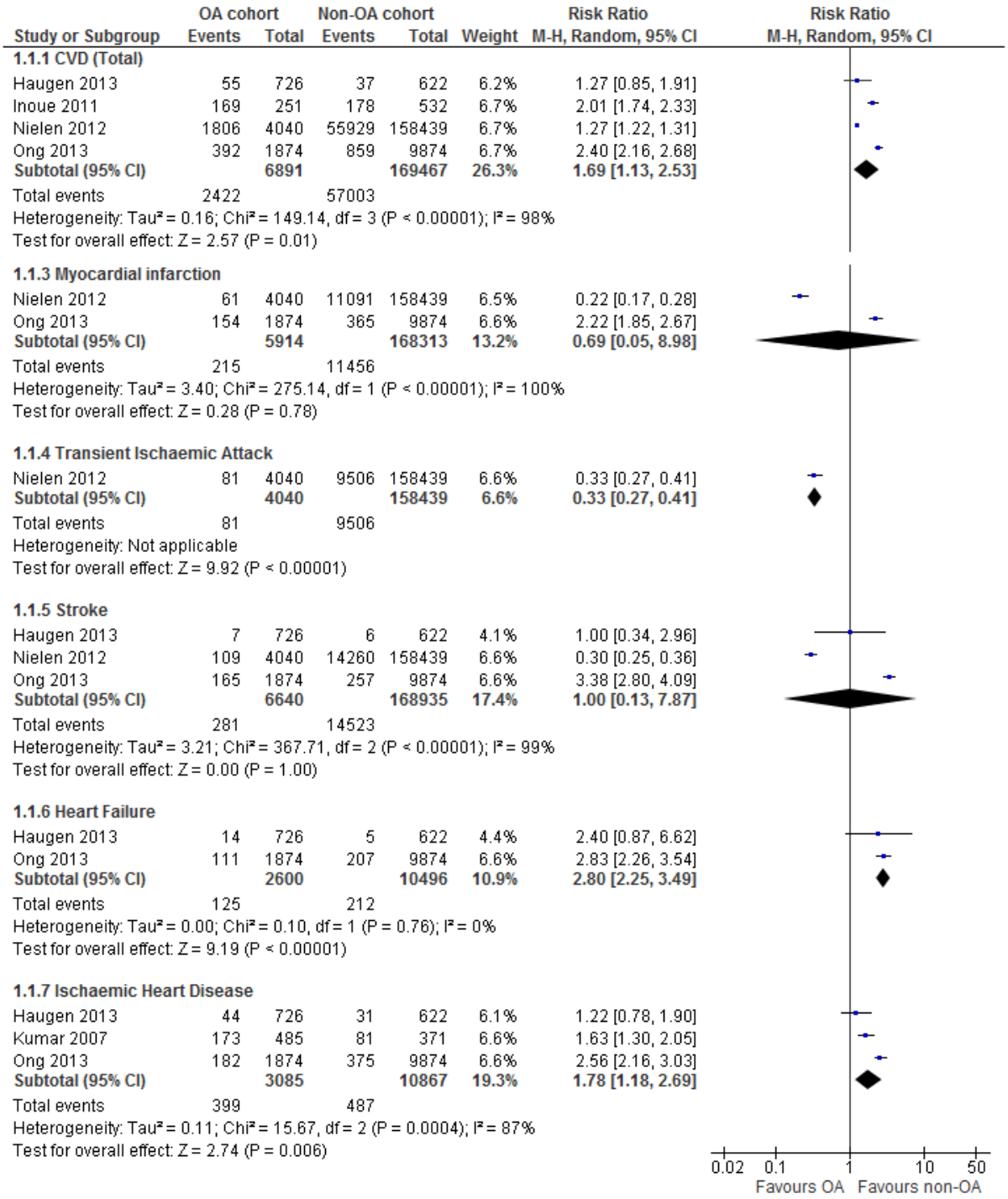

Table 1: Point prevalence of CVD in people with osteoarthritis

CVD	Analysed Studies	Osteoarthritis Cohort		Control Cohort		P-value
		Point Prevalence (95% CI)	Cohort Proportions	Point Prevalence (95% CI)	Cohort Proportions	
Overall CVD	[29,30,33,34]	0.38 (0.37 to 0.40)	2367/6165	0.09 (0.08 to 0.09)	859/9874	0.01
Stroke	[29,30,33]	0.04 (0.04 to 0.05)	281/6640	0.09 (0.09 to 0.09)	15139/168319	1.00
MI	[29,30]	0.04 (0.03 to 0.04)	215/5914	0.07 (0.07 to 0.07)	12118/168313	0.78
HF	[30,33]	0.05 (0.04 to 0.06)	125/2600	0.02 (0.02 to 0.02)	212/10536	<0.001
IHD	[30,33]	0.09 (0.08 to 0.10)	226/2600	0.04 (0.04 to 0.04)	406/10496	0.006
TIA	[29]	0.02 (0.02 to 0.03)	81/4040	0.06 (0.06 to 0.06)	9506/158439	<0.001

CI – confidence intervals; CVD – cardiovascular disease; IHD – ischemic heart disease; HF – heart failure;t MI – myocardial infarct; TIA – transient ischemic attack.

Table 2: Relative risk of CVD occurring compared to non-osteoarthritis control cohorts

CVD	Analysed Studies	Relative risk of occurring compared to non-OA control (95% CI)*	P-value	Cohort	
				Exposed (positive/cohort)	Control (positive/cohort)
Overall CVD	[29,30,33,34]	1.69 (1.13 to 2.53)	0.01	2422/6891	57003/169467
Stroke	[29,30,33]	1.00 (0.13 to 7.87)	1.00	281/6640	14532/168935
MI	[29,30]	0.69 (0.05 to 8.98)	0.78	215/5914	11456/168313
HF	[30,33]	2.80 (2.25 to 3.49)	<0.001	125/2600	212/10496
IHD	[30,33]	1.78 (1.18 to 2.69)	0.006	399/3085	487/10867
TIA	[29]	0.33 (0.27 to 0.41)	<0.001	81/4040	9506/158439

*data based on adjusted analyses.

CI – confidence intervals; CVD – cardiovascular disease; IHD – ischemic heart disease; HF – heart failure; MI – myocardial infarct; TIA – transient ischemic attack.

Supplementary Table 1: Search terms adopted for the MEDLINE search strategy

1. Osteoarthritis
2. Arthriti$
3. Degenerate$
4. OR/1-3
5. Cardiovascular
6. Stroke
7. Cerebrovascular
8. Peripheral vascular
9. Myocardial infarction
10. Coronary heart disease
11. Ischaemic heart disease
12. Atherosclero$
13. Coronary revascularis$
14. Chronic cardiac failure
15. Dementia$
16. Vascular dementia
17. Hypertension
18. Blood pressure
19. Atrial fibrillation
20. Angina
21. Metabolic syndrome
22. Mortality
23. Cardiovascular mortality
24. Death
25. OR/5-25
26. AND/4,25

Supplementary Table 2: Summary of critical appraisal assessment

Study	Appraisal Criterion									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Dahaghin [32]	√	√	√	√	√	√	N/A	√	√	√
Han [17]	√	√	√	√	√	√	N/A	√	√	√
Haugen [33]	√	√	√	√	√	√	N/A	√	√	√
Hoeven [25]	√	√	√	√	√	√	√	√	√	√
Inoue [34]	√	√	√	√	√	√	N/A	√	X	√
Jonsson [22]	√	√	√	X	√	√	N/A	√	√	√
Meek [28]	√	√	√	√	√	√	N/A	√	√	√
Nielen [29]	√	√	√	√	√	√	N/A	√	√	√
Ong [30]	√	√	√	√	√	√	N/A	√	√	√
Rahman [24]	√	√	√	√	√	√	√	√	√	√
Rahman [31]	√	√	√	√	√	√	N/A	√	√	√
Reid [23]	√	√	√	√	X	√	N/A	√	X	√
Singh [35]	√	√	√	√	√	√	N/A	√	√	√
Tsuboi [26]	√	√	√	√	√	√	√	√	X	√
Walston [27]	√	√	√	√	√	√	√	√	√	√

√ - satisfied; X – not satisfied; N/A – not applicable

Critical Appraisal Criteria

1. Did the study address a clearly focused issue?
2. Was the cohort recruited in an acceptable ways?
3. Was the exposure accurately measured to minimise bias?
4. Was the outcome accurately measured to minimise bias?
5. Have the authors identified all important confounding factors?
6. Was the follow-up of the subjects complete enough?
7. Was the follow-up of subjects long enough?
8. Were confidence intervals presented?
9. Were the results generalisable to the general population?
10. Do the results of the study fit with other available evidence?

Supplementary Table 3: Characteristics of included studies

Study (Country)	OA Joints	N (Cases/Control)	Gender (M/F)	Mean Age (Case/Control)	Study details	Assessment of CVD
Dahaghin [32] Netherlands	Multiple joints	3585 (N/S)	1499/2086	Total: 66.6/67.2	Community sample in Rotterdam. OA and Non-OA groups from same cohort.	CV risk factors
Han [17] Korea	Knee	2234 (270/1964)	1020/1214	64.4/53.2	Korean National Health and Nutrition Examination Survey. OA and Non-OA groups from same cohort.	Metabolic syndrome. By Hx, Ex, Ix
Haugen [33] USA	Hand	1348 (726/622)	623/725	Total: 62.8	Framingham Heart Study (Original and Offspring cohorts). Subjects community-based and aged 50–75 years. OA and Non-OA groups from same cohort.	MI, CVA, HF, IHD, HTN, CV mortality
Hoeven [25] Netherlands	Knee, hip, hands	5650 (N/S)	2372/3278	Total: 68.2	Rotterdam Study: community-based prospective population cohort study of the middle aged and elderly. OA and Non-OA groups from same cohort.	HTN, atherosclerosis (by USS carotids)
Inoue [34] Japan	Knee	795 (260/535)	290/500	M: 67.8; F:65.9/M:56.3; F:54.9	Community-based sample. OA and Non-OA groups from same cohort.	Metabolic syndrome. By Hx, Ex, Ix
Jonsson [22] Iceland	Hand	5764 (N/S)	2264/3078	Total: 76.0	AGES Reykjavik Study: population-based ageing study. OA and Non-OA groups from same cohort.	MI, CVA, IHD, HTN, atherosclerosis (by USS: carotid intima media thickness & carotid plaques; CT: calcification of coronary arteries & thoracic aorta)
Meek [28] Netherlands	Multiple joints	5756 (1233 (168 OA)/4523)	2614/3142 (OA: 37/131)	N/S	Two databases assessing CV risk factors from same region in Netherlands. OA cohort seen in clinic and screened for CVD; compared to Doetinchem population-based study (controls)	Observed CV risk factors. By Hx, Ex, Ix
Nielen [29] Netherlands	Multiple joints	175,956 (17,517 (4040 OA)/158,439)	87,147/89,808 (OA:1264/2276)	65.3 (OA:69.8)/51	Netherlands Information Network of GPs. Nationally representative sample. OA and Non-OA groups from same cohort.	MI, TIA, CVA, HTN
Ong [30] USA	Multiple joints	15,295 (5421/9874)	7179/8116 (OA:611/1263)	62.3 (OA:63.9)/54.3	NHANES 1999-2008 nationally-representative database. OA and Non-OA groups from same cohort.	MI, CVA, HF, IHD

Rahman [24] Canada	N/S	49,631 12,745/36,886	20,221/29,410	58.2/57.5	Random sample from Canadian health database. Patients tracked until they received diagnosis for CVD during the study period.	MI, CVA, HF, IHD
Rahman [31] Canada	N/S	81,634 (40,817/40,817)	23,184/58,450	66/66	Random sample from Canadian health database. Patients tracked until they received diagnosis for CVD during the study period.	MI, CVA, HF, IHD
Reid [23] USA	N/S	6299 (N/S)	2835/3464	Total: M:51.7/F:51.7	Native American database surveillance. Both groups recruited and data collected from visits to hospital clinic.	Observed CV risk factors. By Hx, Ex, Ix, assessing Dx and Rx lists
Singh [35] USA	Multiple joints	30,060,457 (OA: 24,345,370)	10,765,031/19,295,426 (OA: 9,015,680/15,329,690)	N/S	Third National Health and Nutrition Examination Survey. OA and Non-OA groups from same cohort.	IHD, CVA and association with HTN
Tsuboi [26] Japan	Hand	789 (244/545)	329/460	68.5/57.6	Cohort study in a rural Japanese community. OA and Non-OA groups from same cohort.	CV mortality
Walston [27] UK	Multiple joints	2,373,551 (175,207) (163,574 OA/2,198,344)	1,109,574/1,263,977 (OA: 61,517/101,757)	Total M:54.5/57.2	UK GP research database. OA and Non-OA groups from same cohort.	MI, CVA, CV mortality

BMI – body mass index; BP - blood pressure; CV – cardiovascular; CVA – cerebrovascular accident; CT – computed tomography; DM – diabetes mellitus; Ex – examination; F – Females; HbA1c - glycosylated haemoglobin; hsCRP – high-sensitivity C-reactive protein ; HF – heart failure; HOMA-IR: homeostasis model assessment of insulin resistance index; HTN – hypertension; Hx - history; IHD – ischemic heart disease; HDL - high-density lipoprotein; Ix – laboratory investigations; LDL - low-density lipoprotein; M – Males; MI – myocardial infarct; N – Numbers; N/S – Not stated; NSAID - non-steroidal anti-inflammatory; N – Numbers; N/S – Not stated; OA- osteoarthritis; Rx – treatment; SES - socioeconomic status; TC - total cholesterol; TIA – transient ischemic attack; TG - triglycerides; UK – United Kingdom; USA – United States of America; USS – ultrasound scan; WC – waist circumference

Supplementary Table 4: Cardiovascular disease risk factors and assessment of CVD in the included studies.

Study	CV Risk Factor	OA - Male	OA - Female	OA - Total	Non-OA - Male	Non-OA - Female	Non-OA - Total
Dahaghin [32]	DM (%) {OR [95% CI]}						
	Age 55-62	-	-	22.8 {1.2 [0.9-1.6]}	-	-	14.2
	Age 62.1-68.7	-	-	28.9 {1.1 [0.7-1.8]}	-	-	27
	Age >68.8	-	-	41.5 {0.9 [0.6-1.4]}	-	-	42.5
	Total	-	-	32 {1.2 [0.9-1.6]}	-	-	27.1
Han [17]	Fasting blood glucose (mg/dl [SD])	99.5 [17.0]	100.0 [18.1]	99.9 [17.9]	100.2 [18.6]	98.3 [17.7]	99.2 [18.2]
	Weight (kg)	65.9 [10.5]	57.3 [8.9]	58.3 [9.5]	66.6 [9.6]	57.5 [8.5]	62.0 [10.1]
	BMI (kg/m2)	23.4 [3.6]	24.8 [3.2]	24.6 [3.3]	23.7 [2.9]	23.9 [3.2]	23.8 [3.1]
	Current smoker (%)	46.3	9.2	14.8	54.6	5.6	30
	Ex-smoker (%)	41.5	1.7	7.8	23.9	0.9	12.4
	Alcohol consumption (%)	85.4	43.2	49.6	83.4	4.6	66.4
	Exercise (%)	31.7	19.7	21.6	34.7	25.8	30.2
	HDL cholesterol (mg/dl) [range]	153.9 [80.5]	45.5 [9.8]	45.0 [10.2]	163.4 [84.4]	47.5 [10.2]	45.5 [10.3]
	Systolic BP (mmHg) [range]	132.8 [20.5]	133.3 [21.0]	133.2 [20.9]	128.7 [19.3]	124.0 [20.7]	126.4 [20.2]
Haugen [33]	High blood glucose (%)	-	-	7.7; **9.1**	-	-	6.1
	BMI (kg/m2) [SD]	-	-	28.0 [4.4]; **27.8[4.9]**	-	-	27.4 [4.5]
	TC:HDL ratio [SD]	-	-	4.5 [1.4]; **4.5 [1.4]**	-	-	4.6 [1.6]
	Hypertension (%)	-	-	10.2; **8.9**	-	-	5
	Anti-HTN meds. (%)	-	-	38.3; **33.3**	-	-	19.8
	Lipid-lowereing meds. (%)	-	-	14.5; **9.8**	-	-	9.5
	NSAID meds.(%)	-	-	18.8; **11.5**	-	-	10.6
	Anti-diabetic meds. (%)	-	-	5.9; **4.6**	-	-	2.6
	Daily aspirin use (%)	-	-	24.5; **23.6**	-	-	14.1
	Alcohol consumption (%)	-	-	64; **63.5**	-	-	68.4

	Smoking (%)	-	-	37.6; **40.6**	-	-	50.8
	Inactivity (%)	-	-	36.8; **35.1**	-	-	30.7
Hoeven [25]	None Documented	-	-	-	-	-	-
Inoue [34]	Diabetes mellitus (%)	4	9	13	19	3	22
	HbA1c (%) [range]	5.3 [0.5]	5.3 [0.8]	-	5.3 [0.7]	5.1 [0.3]	-
	BMI (kg/m2) [range]	23.6 [2.8]	23.8 [3.6]	-	23.5 [2.7]	22.3 [2.7	-
	Waist circumference (cm) [range]	84.5 [7.9]	85.2 [9.6]	-	84.6 [7.4]	80.5 [8.2]	-
	Smoking (%)	19.2	2.4	-	33.7	11.6	-
	Alcohol consumption (%)	80.8	12.5	-	73.7	25.7	-
	Exercise (%)	19.2	32.2	-	30	26	-
	HDL cholesterol (mg/dl) [range]	59.7 [17.6]	62.2 [14.9]	-	55.9 [15.2]	64.2 [14.2]	-
	Triglyceride (mg/dl) [range]	80.9 [40.4]	90.1 [44.6]	-	134.4 [119.0]	80.8 [41.0]	-
	Hyperlipidaemia (%)	11.5	22.1	-	9.1	8.6	-
	Systolic BP (mmHg) [range]	137.6 [18.4]	130.7 [18.6]	-	128.9	120	-
	Hypertension (%)	23.1	15.4	-	23.5	17.8	-
	Metabolic syndrome (%)	23.1	15.4	-	22.2	5.1	-
Jonsson [22]	None Documented	-	-	-	-	-	-
Meek [28]	BMI (kg/m2)	-	-	29.1	-	-	26.6
	BMI >25 (%)	-	-	80.5	-	-	61.9
	BMI >30 (%)	-	-	34	-	-	17.3
	Total cholesterol (mmol/l)	-	-	5.53	-	-	5.58
	Total cholesterol >6.5 mmol/l (%)	-	-	15.9	-	-	16.3
	HDL cholesterol (mmol/l)	-	-	1.47	-	-	1.43
	HDL cholesterol <0.9 mmol/l (%)	-	-	8.1	-	-	8.2
	TC:HDL ratio	-	-	4	-	-	4.2
	Lipid-lowering medication use (%)	-	-	13.1	-	-	10.1
	Abnormal lipid profile incl. med	-	-	35.5	-	-	31.5

	(%)						
	Ever smoker (%)	-	-	61.1	-	-	62.7
	Current smoker (%)	-	-	20.6	-	-	20.5
	Systolic BP (mmHg) [range]	-	-	146.7	-	-	135.7
	BP >140/90 or anti-HTN use (%)	-	-	68.1	-	-	56
Nielen [29]	Diabetes mellitus (%)	-	-	16.5	-	-	-
	Hypercholesterolaemia (%)	-	-	13.3	-	-	4.8
	Hypertension (%)	-	-	38.5	-	-	13.3
Ong [30]	HbA1c (%) [range]	-	-	5.61 [5.56-5.65]	-	-	5.49 [5.46-5.52]
	Fasting blood glucose (mmol/L) [range]	-	-	5.90 [5.80-6.00]	-	-	5.83 [5.78-5.87]
	Fasting insulin (mU/L) [range]	-	-	7.74 [7.19-8.33]	-	-	7.21 [6.91-7.53]
	HOMA-IR* [range]	-	-	2.03 [1.88-2.20]	-	-	1.87 [1.78-1.96]
	HbA1c multiple regression analysis	-	-	0.38 [0.08-1.31]	-	-	-
	BMI (kg/m2)	-	-	29.7	-	-	28.2
	HDL cholesterol (mmol/l)	-	-	1.43	-	-	1.38
	LDL cholesterol (mmol/l)	-	-	3.11	-	-	3.22
	Triglyceride (mmol/l) [range]	-	-	1.52 [1.45-1.60]	-	-	1.42 [1.38-1.45]
	Total cholesterol (mmol/l)	-	-	5.37	-	-	5.38
	Lipid-lowering meds.(%)	-	-	28.7	-	-	16.1
	Systolic BP (mmHg)	-	-	131.3	-	-	126
	Hypertension (%)	-	-	58.9	-	-	37.5
	Current smoker (%)	-	-	14.1	-	-	20.9
	Ex-smoker (%)	-	-	39.3	-	-	29.4
	Alcohol consumption (%)	-	-	26.4	-	-	35
Rahman [24]	Diabetes mellitus (RR)[95% CI]{%}						
	Age <65	2.05 [1.70-1.22]	2.30 [1.89-2.80]	1.73 [1.60-1.88]{5.2}	-	-	{4.7}
	Age >65	1.50 [1.29-1.74]	1.79 [1.56-2.05]	-	-	-	-

	Hyperlipidaemia (%)	-	-	6	-	-	4.9
	BMI 25-29.9 (%)	-	-	32.1	-	-	36.7
	BMI >30 (%)	-	-	34.4	-	-	17.7
	Hypertension (%)	-	-	19.7	-	-	16.4
Rahman [31]	BMI >30 (OR)[95% CI]{%}	1.23 [1.04-1.45]	1.09 [0.96-1.23]	1.14 [1.03-1.26]{11.5}	-	-	9.9
	BMI 25-29.9 (OR)[95% CI]{%}	1.09 [0.95-1.24]	0.94 [0.84-1.04]	0.99 [0.92-1.08]{32.1}	-	-	29.7
	Current smoker (OR)[95% CI]{%}	1.40 [1.16-1.69]	1.09 [0.96-1.25]	1.16 [1.04-1.29){19.7}	-	-	19
	Ex-smoker (OR)[95% CI]{%}	1.39 [1.20-1.61]	1.16 [1.06-1.26]	1.19 [1.11-1.29]{49.6}	-	-	46.6
	Inactivity (OR)[95% CI]{%}	1.28 [1.11-1.48]	1.37 [1.20-1.26]	1.33 [1.21-1.47]{60.6]	-	-	58.5
	Diabetes mellitus (OR)[95% CI]{%}	1.80 [1.57-2.06]	1.96 [1.76-2.19]	1.90 [1.75-2.01]{11.5}	-	-	9.9
	Hypertension (OR)[95% CI]{%}	1.92 [1.72-2.14]	2.01 [1.84-2.18]	1.98 [1.86-2.12]{36.7}	-	-	32.1
Reid [23]	DM (OR)[95% CI]						
	Age 35-44	1.36 [0.66-2.80]	1.90 [1.06-3.40]		-	-	-
	Age 45-54	1.04 [0.62-1.74]	1.62 [1.09-2.42]		-	-	-
	Age 55-64	0.60 [0.35-1.01]	1.31 [0.87-1.99]		-	-	-
	Age >65	1.63 [1.00-2.67	1.25 [0.80-1.94]		-	-	-
	Hypertension (OR)[95% CI]						
	Age 35-44	4.07 [1.94-8.51]	2.65 [1.54-4.54]		-	-	-
	Age 45-54	5.35 [2.81-10.17]	5.40 [3.36-8.66]		-	-	-
	Age 55-64	8.79 [3.98-19.38]	4.24 [2.50-7.21]		-	-	-
	Age >65	12.63 [5.25-30.37]	8.46 [4.81-14.90]		-	-	-
	BMI 25.0-29.9 (OR)[95% CI]						
	Age 35-44	0.93 [0.18-4.82]	1.36 [0.58-3.19]		-	-	-
	Age 45-54	2.79 [0.80-9.78]	1.14 [0.52-2.51]		-	-	-
	Age 55-64	1.26 [0.37-4.24]	1.45 [0.65-3.26]		-	-	-
	Age >65	1.21 [0.58-2.54]	0.86 [0.47-1.57]		-	-	-

	BMI 30-34.9 (OR)[95% CI]						
	Age 35-44	1.38 [0.29-6.51]	0.99 [0.40-2.44]		-	-	-
	Age 45-54	2.12 [0.60-7.51]	1.56 [0.74-3.28]		-	-	-
	Age 55-64	2.05 [0.63-6.72]	2.01 [0.90-4.46]		-	-	-
	Age >65	1.03 [0.47-2.25]	0.95 [0.52-1.73]		-	-	-
	BMI 35-39.9 (OR)[95% CI]{%}						
	Age 35-44	1.02 [0.2-5.37]	0.82 [0.31-2.13]		-	-	-
	Age 45-54	2.88 [0.78-10.61]	2.00 [0.94-4.26]		-	-	-
	Age 55-64	2.51 [0.73-8.66]	3.88 [1.73-8.70]		-	-	-
	Age >65	1.35 [0.54-3.39]	0.43 [0.20-0.93]		-	-	-
	BMI >40 (OR)[95% CI]{%}						
	Age 35-44	2.95 [0.60-14.53]	2.01 [0.86-4.68]		-	-	-
	Age 45-54	3.31 [0.91-12.03]	2.40 [1.12-5.14]		-	-	-
	Age 55-64	3.94 [1.07-14.51]	3.09 [1.38-6.94]		-	-	-
	Age >65	1.06 [0.38-2.97]	1.33 [0.60-2.94]		-	-	-
	Current Smoker (OR)[95% CI]						
	Age 35-44	1.96 [1.03-3.74]	1.75 [1.04-2.97]		-	-	-
	Age 45-54	1.30 [0.76-2.21]	1.52 [1.01-2.30]		-	-	-
	Age 55-64	2.05 [1.20-3.52]	2.15 [1.34-3.47]		-	-	-
	Age >65	2.99 [1.52-5.89]	1.25 [0.63-2.47]		-	-	-
Singh [35]	None Documented	-	-	-	-	-	-
Tsuboi [26]	BMI (kg/m2) [range]	-	-	24.8 [3.2]	-	-	23.6 [3.0]
	Smoking (%)	-	-	21.3	-	-	31
	Alcohol consumption (%)	-	-	18	-	-	27
	Exercise (%)	-	-	22.5	-	-	24
Walston [27]	None Documented	-	-	-	-	-	-

BMI – body mass index; BP - blood pressure; CV – cardiovascular; CVA – cerebrovascular accident; CT – computed tomography; DM – diabetes mellitus; Ex – examination; HbA1c - glycosylated haemoglobin; hsCRP – high-sensitivity C-reactive protein ; HF – heart failure; HOMA-IR: homeostasis model assessment of insulin resistance index; HTN – hypertension; Hx - history; IHD – ischemic heart disease; HDL - high-density lipoprotein; Ix – laboratory investigations; LDL - low-density lipoprotein; MI – myocardial infarct; NSAID - non-steroidal anti-inflammatory; N – Numbers; N/S – Not stated; Rx – treatment; SES - socioeconomic status; TC - total cholesterol; TIA – transient ischemic attack; TG - triglycerides; WC – waist circumference; USS – ultrasound scan.