Associations between cardiovascular disease severity, osteoarthritis co-morbidity and physical health: a population-based study

James A. Prior¹, Kelvin P. Jordan¹ and Umesh T. Kadam¹,²

Abstract

Objective. The aim of this study was to investigate the interaction between cardiovascular disease severity and OA co-morbidity on physical health.

Methods. A baseline questionnaire was mailed to 9676 patients aged ≥ 40 years from UK family practices. A priori exclusive morbidity groups were constructed as follows, based on records 3 years before baseline: (i) reference group—neither cardiovascular disease nor OA; (ii) cardiovascular disease severity index groups—with hypertension, ischaemic heart disease or heart failure without OA; (iii) OA index group without cardiovascular disease and (iv) co-morbid severity groups with hypertension, ischaemic heart disease or heart failure with OA. Adjusted associations between morbidity groups and physical health [mean physical component summary (PCS) score based on the 12-item Short Form Health Survey (SF-12)] compared with the reference group were assessed using linear regression methods.

Results. A total of 5426 patients responded to the baseline questionnaire (56% response). The adjusted mean difference in PCS score between the reference group and the cardiovascular disease index were −2.4 (95% CI −3.4, −1.4) for hypertension, −5.3 (−6.3, −4.3) for ischaemic heart disease and −11.8 (−13.6, −9.9) for heart failure. The difference in the score for the index OA group was −5.6 (−6.5, −4.6). Estimates for co-morbid OA groups were −6.8 (−7.9, −5.7) for hypertension, −9.1 (−10.6, −7.6) for ischaemic heart disease and −12.8 (−16.0, −9.7) for heart failure.

Conclusion. In cardiovascular populations with differing severity, the co-morbid addition of OA was associated with incrementally poorer physical health, but such interactions were less than additive.

Key words: cardiovascular diseases, cohort studies, co-morbidity, chronic disease, osteoarthritis.

Introduction

In ageing populations there is an increasing prevalence of chronic diseases [1], and as the likelihood of having one chronic disease increases in an individual, so does the chance of experiencing two or more chronic diseases at the same time [2]. Co-morbidity, the experiencing of an additional disease along with an index disease [3], is associated with poorer quality of life [4], increased mortality [5] and increased health care utilization [4]. However, the focus of current research has frequently been to measure any co-morbidity based either on simple counts or broad constructs of disease such as cardiovascular disease (CVD) or musculoskeletal (MSK) disorders [6]. Such approaches do not incorporate the fact that there are different stages of chronic disease, nor that the specific combinations may have differing influences on health and health care. Research into specific chronic disease combinations with a priori hypotheses and their subsequent influence on physical health remains very limited.

Two common chronic diseases in older populations are CVD and OA. Patients with OA have been shown to experience some of the highest levels of co-morbidity in family practice [7] and CVD and OA commonly co-occur in the same individual. A recent study of co-morbid disease combinations in Dutch primary care found 23% of coronary heart disease patients and 24% of heart failure (HF) patients had OA, forming one of the most prevalent
co-morbidities [8]. This co-occurrence is not fully explained by increasing age, and it has been postulated that there may be shared pathogenic mechanisms [9, 10].

OA co-morbidity is also associated with poor quality of life [11] and CVD co-morbidity is associated with poor clinical outcomes [12] and with increased risk of mortality [13]. Although research has shown the importance of interaction between OA and co-morbidity in populations [11–14], there is still little evidence on interactions between specific chronic diseases and the consequences on health and health care outcomes. Interaction is the interdependent operation of two or more causes to produce, prevent or control an effect [15, 16]. Interaction may take the form of an additive effect, which is the actual effect of two factors occurring together, being the sum of the individual effects that would be produced by each of the factors in the absence of the other [17]. Interaction is important to understand, as it provides the opportunity to identify and target co-morbidity and tailor potential interventions to prevent health deterioration [1, 2].

Current evidence has also shown that different chronic disease populations have differing levels of health impact. For example, in populations, hypertension has less of an adverse influence on health than ischaemic heart disease (IHD), which has less of an impact than HF [18]. So in populations, there is the concept of relative severity, which can be attributed to the different morbidities within each chronic disease spectrum. In previous studies using this conceptual approach in populations we have shown that increasing co-morbidity defined by relative severity in OA was associated with poorer physical health [11]. Additional studies also show that different morbidities within CVD and MSK spectra are associated with poor physical health [18, 19]. Maintaining the general physical health of increasingly ageing populations is important to ensure that prolonged life remains of good quality.

The key questions that remain to be addressed are (i) what is the interaction between specific CVD and OA on physical health in populations, and is such interaction additive, and (ii) does a priori allocation of CVD severity to populations with co-morbid OA influence physical health incrementally?

The Comorbidity Cohort (2C) study was designed to investigate three exclusive CVD severity groups with co-morbid OA and their influence on health and health care in family practice populations. The core a priori hypothesis investigated in this baseline article was that increasing CVD severity and the addition of OA would be associated with an additive effect of poorer physical health in family practice populations compared with index CVD populations.

Patients and methods

Study population

Patients ≥ 40 years of age were recruited from 10 family practices from North Staffordshire and Cheshire, UK. These practices are part of a local research network that is linked to the Arthritis Research UK Primary Care Centre at Keele University. Practices have a high level of morbidity coding in routine clinical consultations, particularly chronic disease registers.

Study design

The 2C study was prospectively designed to investigate the interaction between CVD and OA by using repeated measures of self-reported health linked to patient clinical data. Family practice populations were mailed study invitations (on their practice’s letterhead) by the research team. A postal questionnaire accompanied the invitation and was used to obtain baseline information on general health, pain-specific measures of CVD and OA and also study consent. The overall study design also consisted of shorter monthly health questionnaires and a repeat of the main questionnaire, which was sent at the 12-month follow-up, details of which are reported elsewhere [20]. Ethics approval for the 2C study was granted by Cheshire Research Ethics Committee (reference number 09/H1017/40).

Morbidity groups

The morbidity groups were sampled from family practice and the selection was based on computerized clinical records. In UK family practice, Read codes [21] are used to classify the morbidity of patients when they present in consultation or when clinical data are coded. Specific code sets for conditions such as CVD and OA covering a 3-year time period (starting from November 2006) before the baseline questionnaire were searched for. A priori populations with exclusive CVD categories were constructed in severity order [22] from hypertension (least severe) to IHD to HF (most severe). The choice of three clearly defined CVDs allowed the examination of relative morbidity severity within the same chronic disease spectrum. In the same 3-year time period before the baseline questionnaire, patients with an OA diagnosis in their clinical records were also identified. This broader definition of OA was based on coded clinical data and included either diagnostic labels for any OA-related joint problem or radiographic-related diagnosis. By considering three CVD groups with the addition of generalized OA, which is the normal feature in populations, in contrast to joint-specific OA [23], this allowed a feasible test of the co-morbid interaction between few, but specific disease combinations.

Using the presence or absence of a CVD or OA diagnosis, a total of eight exclusive morbidity groups were constructed within four overall study groups: (i) a randomly selected reference group of patients without CVD or OA, (ii) three index CVD groups without OA [hypertension (randomly selected), IHD and HF], (iii) a randomly selected index OA group without any of the CVD morbidities and (iv) three CVD (hypertension, IHD and HF) co-morbid groups with OA (Table 1). All index CVD and CVD co-morbid groups were exclusive. Therefore, if a patient had a record of more than one of the three CVD morbidities, they were placed into the most severe group, e.g. a
Table 1  Descriptions and abbreviations of eight morbid-
group

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Morbidity group description</th>
<th>Morbidity group abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference group</td>
<td>No CVD or OA</td>
<td>−CVD−OA</td>
</tr>
<tr>
<td>Four index groups</td>
<td>Hyp, but no OA</td>
<td>+Hyp−OA</td>
</tr>
<tr>
<td></td>
<td>IHD but no OA</td>
<td>+IHD−OA</td>
</tr>
<tr>
<td></td>
<td>HF but no OA</td>
<td>+HF−OA</td>
</tr>
<tr>
<td></td>
<td>OA but no CVD</td>
<td>−CVD+OA</td>
</tr>
<tr>
<td>Three co-morbid groups</td>
<td>HYP and OA</td>
<td>+Hyp+OA</td>
</tr>
<tr>
<td></td>
<td>IHD and OA</td>
<td>+IHD+OA</td>
</tr>
<tr>
<td></td>
<td>HF and OA</td>
<td>+HF+OA</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; Hyp: hypertension; IHD: ischaemic heart disease; HF: heart failure; +: positive; −: negative.

patient who had a record of hypertension and HF over the 3-year time period would be placed in the HF group.

Baseline health measurement

The 12-item Short Form Health Survey (SF-12) [24] was used to measure self-reported general health. It is a widely used instrument that has been applied in the assessment of health in different chronic diseases and allows comparison between them. From this measure, the primary outcome was the physical component summary (PCS) score. The PCS score is normalized to the US general population to a score of 50; below or above this represents poorer or better physical health, respectively, than this population. In addition, a separate question from the baseline questionnaire was used to establish the frequency with which the study sample had experienced pain in any of 11 different body sites (neck, shoulder, elbow, hand, back, hip, knee, foot, chest, abdominal and headache) [25, 26].

Other study sample data collected in the baseline questionnaire included age, gender, deprivation status and BMI. The measure of deprivation was based on the 2007 Index of Multiple Deprivation (IMD) [27].

Statistical analysis

The morbidity groups were categorized by age, gender, deprivation status and BMI. Age was categorized into five groups: 40–49, 50–59, 60–69, 70–79 or ≥ 80 years. IMD status was categorized into three groups: those with the 20% least deprived scores, the 20% most deprived scores and the middle 60%. BMI was dichotomized into those with a BMI ≤ 25 (underweight or normal weight) or ≥ 26 (overweight or obese).

The frequency of pain was converted from a categorical response for each location to a yes or no response for the experience of any pain in each location in the 4 weeks prior to the baseline questionnaire. From this list, each patient then had a mutually exclusive value ranging from 0 (no pain) to 11 (pain in 11 body sites), forming the pain measure as the number of pain sites.

For each morbidity group, the mean baseline PCS score with the 95% CI was assessed. The associations between morbidity groups and physical health compared with the reference group were estimated using linear regression analysis, expressed as the mean difference in PCS scores (95% CI). These analyses are presented as (i) unadjusted values; (ii) adjusted for age, gender and deprivation status; (iii) further adjustment including BMI and (iv) final adjustment for age, gender, deprivation status, BMI and number of pain sites.

The design of the 2C study allowed us to examine how the observed estimates of the mean difference in PCS scores between each morbidity group and the reference group differed from that expected. Since we had the adjusted mean differences for the index CVD groups and index OA group, we could calculate the expected mean differences for each of the CVD groups with co-morbid OA by adding the figures for the index groups and comparing them with the observed mean differences. The difference between the observed and expected estimates in this additive approach enabled assessment of the interaction between CVD and OA.

Results

Of the 9676 patients invited to participate in the 2C study, the reference group accounted for 26%. The three index CVD groups without OA accounted for 14% (hypertension), 21% (IHD) and 3% (HF) and the index OA group for 14% of the study population. The three CVD groups with OA accounted for 17% (hypertension), 5% (IHD) and 1% (HF).

From this denominator population, 5426 (56%) patients responded to the baseline questionnaire. Of the responders, there were 1141 (22%) patients in the reference group. In the CVD index groups there were 688 (13%) patients with hypertension, 1140 (22%) with IHD and 141 (3%) with HF. There were 788 (15%) in the OA index group. Figures for the CVD co-morbid groups with OA were 953 (18%) with hypertension, 284 (6%) with IHD and 41 (1%) with HF.

Characteristics of the morbidity groups

The mean age of the overall sample was 67 years (s.d. 12) and the reference group was the youngest, with a mean age of 57 years (s.d. 10). More than half of the patients from the IHD and HF index groups and all three co-morbid groups were ≥ 70 years of age (Table 2). Only the IHD and HF index groups had more men than women. In terms of deprivation status, only the HF index group and HF co-morbid group were more likely to be from the most deprived population. Across all morbidity groups, >60% were overweight or obese, and these proportions were greatest in the co-morbid groups.
Baseline physical health

Patients in the reference group had the best physical health, with a mean PCS score of 49.7 (95% CI 49.1, 50.2) (Table 3). Compared with the reference group, increasing CVD severity was associated with worsening physical health. The mean PCS scores were 43.3 (95% CI 42.4, 44.2) for hypertension, 38.1 (37.5, 38.8) for IHD and 30.6 (28.9, 32.3) for HF. The OA index group also had worse physical health than the reference group, with a mean PCS score of 38.8 (95% CI 38.0, 39.7), which was similar to the index IHD group.

The CVD co-morbid groups had lower PCS scores than the index groups. The mean PCS scores for CVD co-morbid groups with OA were 34.7 (95% CI 34.0, 35.5) for hypertension, 31.2 (30.0, 32.5) for IHD and 26.9 (23.8, 30.0) for HF (Table 3 and Fig. 1).

Associations between morbidity groups and physical health

Compared with the reference group, the mean difference in PCS scores for the three CVD index groups, when adjusted for age, gender and deprivation status, were −3.1 points (95% CI −4.2, −2.0) for hypertension, −8.3 (−9.3, −7.2) for IHD and −13.8 (−15.8, −11.8) for HF (Table 3). The mean difference for the index OA group was −8.6 (95% CI −9.6, −7.5). Compared with the reference group, the adjusted mean difference in PCS score was −10.7 points (95% CI −11.8, −9.6) for the hypertension and OA co-morbid group, −13.2 (−14.8, −11.7) for the IHD co-morbid group and −16.0 (−19.3, −12.7) for the HF co-morbid group. Adjusting for age, gender and deprivation diminished the strength of association between all groups and poor physical health, but the mean differences remained significantly different from the reference group.

When adjusting for BMI, this factor was shown to account for some of the poor physical health, with a decrease of 0.4–1.4 points across all morbidity groups. The final adjustment to include the number of pain sites saw a further decrease in each morbidity group, although each remained significantly poorer than the reference group: −2.4 points (95% CI −3.4, −1.4) for hypertension, −5.3 (−6.3, −4.3) for IHD and −11.8 (−13.6, −9.9) for IHD (Table 3). The mean difference for the index OA group was −5.6 (95% CI −6.5, −4.6). Compared with the reference group, the adjusted mean difference in PCS score was −6.8 points (95% CI −7.9, −5.7) for the hypertension and OA co-morbid group, −9.1 (−10.6, −7.6) for the IHD co-morbid group and −12.8 (−16.0, −9.7) for the HF co-morbid group.

The expected additive estimates were −2.4 (index hypertension) + −5.6 (index OA) = −8.0 for the hypertension co-morbid group, −5.3 (index IHD) + −5.6 (index OA) = −10.9 for the IHD co-morbid group and −11.8 (index HF) + −5.6 (index OA) = −17.4 for the HF co-morbid group. However, the observed CVD co-morbid estimates were −6.8, −9.1 and −12.8, respectively. The comparison between expected and observed estimates shows that the co-morbid interaction was actually less than additive (Fig. 2).

2C baseline responder characteristics

Detailed characteristics of the 2C study morbidity groups, responders and non-responders have been previously reported [20]. Responders were older and had a more
### Table 3 Associations between morbidity groups and physical health

<table>
<thead>
<tr>
<th>Morbidity group</th>
<th>Study sample, n (%)</th>
<th>Age, mean (s.d.), years</th>
<th>PCS score, mean (95% CI)</th>
<th>Linear regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference -CVD-OA</td>
<td>1141 (22)</td>
<td>57 (10)</td>
<td>49.7 (49.1, 50.2)</td>
<td>[</td>
</tr>
<tr>
<td>Index +Hyp-OA</td>
<td>688 (13)</td>
<td>67 (11)</td>
<td>43.3 (42.4, 44.2)</td>
<td>-6.3 (-7.4, -5.3)</td>
</tr>
<tr>
<td>+IHD-OA</td>
<td>1140 (22)</td>
<td>71 (10)</td>
<td>38.1 (37.5, 38.8)</td>
<td>-11.5 (-12.5, -10.6)</td>
</tr>
<tr>
<td>+HF-OA</td>
<td>141 (3)</td>
<td>76 (11)</td>
<td>30.6 (28.9, 32.3)</td>
<td>-19.0 (-21.0, -17.0)</td>
</tr>
<tr>
<td>-CVD+OA</td>
<td>788 (15)</td>
<td>65 (11)</td>
<td>38.8 (38.0, 39.7)</td>
<td>-10.8 (-11.9, -9.8)</td>
</tr>
<tr>
<td>Co-morbid +Hyp-OA</td>
<td>953 (18)</td>
<td>71 (9)</td>
<td>34.7 (34.0, 35.5)</td>
<td>-14.9 (-15.9, -13.9)</td>
</tr>
<tr>
<td>+IHD-OA</td>
<td>284 (6)</td>
<td>75 (9)</td>
<td>31.2 (30.0, 32.5)</td>
<td>-18.4 (-19.9, -16.9)</td>
</tr>
<tr>
<td>+HF-OA</td>
<td>41 (1)</td>
<td>60 (8)</td>
<td>26.9 (23.8, 30.0)</td>
<td>-22.8 (-26.3, -19.2)</td>
</tr>
</tbody>
</table>

Health measured by the mean physical component summary (PCS) score. Deprivation status measured using the indices of multiple deprivation (IMD). Number of pain sites was the number of joint sites where pain occurred at least once over a 4-week period. The number who reported no pain or pain at at least one joint site = 5085, number for whom a BMI as available = 4841. CVD: cardiovascular disease; Hyp: hypertension, IHD: ischaemic heart disease; HF: heart failure; +: positive; −: negative.
affluent status, but there was no difference in gender distribution between the baseline sample and responders (see supplementary Table S1, available at Rheumatology Online).

Discussion

Our study shows that CVD severity and co-morbid OA were associated with incrementally poor physical health, and such interactions were less than additive. Factors such as age, gender, deprivation status, BMI and number of pain sites did not fully explain the associations. The implications of these findings are that in populations both chronic disease severity and chronic disease co-morbidity are important influences on poor physical health, and both need to be taken into account in developing strategies aimed at either improvement of physical health or prevention of physical health deterioration.

Studies of interaction are important [11, 14, 28], as they provide the potential for targeted intervention of the key co-morbidity that leads to greater deterioration in the health of a population with an index disease. While there is long-standing research of the concept of interaction in causal epidemiology, specifically in relation to mortality [29, 30], very few studies have investigated this in the co-morbidity literature in relation to health. An additional key possibility raised by the 2C study is that acquiring one chronic disease is associated with the primary health deterioration, but additional chronic disease leads to further smaller and gradual accrual of health deficit. However, such a hypothesis would require further prospective investigation, as instruments such as the SF-12 may be prone to floor effects, whereby chronic disease patients cannot report any worse health with the addition of other morbidities. This could explain why the addition of OA to the most severe CVD had a small impact on physical health.

To our knowledge, while there are developing cohort studies investigating co-morbidity [31–33], there have been no studies that have been innovatively designed a priori to test the interaction between specified common chronic diseases of ageing (CVD and OA). The baseline 2C study findings are externally comparable to other chronic disease and physical health studies. International CVD studies in the general population, using the SF surveys, have also shown similar physical health estimates in index hypertension, IHD and HF populations [34–36]. Index OA studies in the general population have shown SF physical health estimates comparable to our study [37, 38]. These studies, added to our previous and current investigations, show that the concept of relative morbidity severity in populations can be applied to a chronic disease such as CVD, providing the evidence to inform public health policy in the care of people who have multiple chronic diseases at the same time.

Ascertainment of the 2C study population from routinely collected family practice data means that such severity can be based on chronic disease registers, which provides a simple and practical basis for identifying populations with poorer physical health. For clinicians, in CVD populations, OA may identify a subgroup of patients more vulnerable to poor physical health. These types of subgroup need to be managed with potential new, tailored interventions that improve access to the most at-risk patients [39, 40], are applicable to both conditions [41] and so might target important factors such as BMI and exercise, as well as optimal management of each condition [42, 43].
Strengths
The 2C study design incorporated eight morbidity groups to hypothesis test specific co-morbid interactions in relation to self-reported overall health. Although each group was also likely to have other morbidities alongside CVD and OA, this issue of other co-morbidities was addressed by the study design. Since index and co-morbid groups were selected from the same population, index morbidity groups provided matched populations to the co-morbidity groups. Although the more severe, and often older, morbidity groups may have had more other co-morbidities, the adjustment for age also acted as a proxy adjustment for co-morbidity, meaning the specific interaction between the CVD groups and OA was tested. Further still, major confounders were adjusted for, including number of pain sites, which accounted for multiple joint problems, likely in the OA group. This demonstrated that the poor physical health was not just a result of multiple joint pains, but the interaction of CVD and OA.

Limitations
While the SF-12 is a widely used and valid generic measure of health, there may be limitations in its ability to record the status of the oldest populations with the poorest health [44]. Adjustment for the number of pain sites allowed consideration of multiple bodily pain. This approach provides some explanation of (potentially OA related) pain [23], but further research is still required to understand joint-specific OA co-morbid with CVD and what the specific impacts might be. However, subtyping OA categories would have required a significantly increased study sample size.

The other factor in the analytical approach is other modifying factors, such as drug therapies. In the careful design of the eight selected groups, the individual CVD groups provide comparable populations to CVD groups with OA. Thus the CVD medications are likely to be similar, and the OA referent group provides the proxy for potential analgesia use. So again, while a detailed analysis would include medication, the design allows for a reasonable comparison. Future analysis should take account of medication as a modifier in the relationship between CVD, OA and physical health.

Finally, the study findings need to be interpreted in the light of the people who participate in health surveys. Non-responders were typically younger and had a more deprived status than responders [20], limiting the generalizability of these findings. However, setting these findings in the context of external evidence of index morbidities suggests that our study’s original findings remain valid.

Conclusions
CVD severity and co-morbid OA were associated with incrementally poorer physical health in family practice populations, and such interactions were less than additive. Disease severity allocated a priori to the CVD population showed that the exclusive combination of hypertension, IHD and HF with co-morbid OA was associated with increasing levels of poorer health. Population disease severity and co-morbidity, based on routinely collected clinical registers, show that they are both important influences on adverse physical health. Such approaches provide practical methods for identifying patients at risk of poor and deteriorating health and developing models for co-morbid health care in patients with chronic disease such as CVD and OA in ageing populations.

Supplementary data
Supplementary data are available at *Rheumatology* Online.

Rheumatology key messages
- All cardiovascular disease severity groups with co-morbid OA showed worse physical health than respective index groups.
- Interaction between cardiovascular disease and OA and adverse physical health is less than additive.
- Identifying specific chronic disease combinations provides the opportunity for targeted and tailored health care interventions.

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