Socio-economic status and the risk of developing hand, hip or knee osteoarthritis: a region-wide ecological study


Objective: To determine the association between socio-economic status (SES) and risk of hand, hip or knee osteoarthritis (OA) at a population level.

Design: Retrospective ecological study using the System for the Development of Research in Primary Care (SIDIAP) database (primary care anonymized records for >5 million people in Catalonia (Spain)). Urban residents >15 years old (2009–2012) were eligible. Outcomes: Validated area-based SES deprivation index MEDEA (proportion of unemployed, temporary workers, manual workers, low educational attainment and low educational attainment among youngsters) was estimated for each area based on census data as well as incident diagnoses (ICD-10 codes) of hand, hip or knee OA (2009–2012). Zero-inflated Poisson models were fitted to study the association between MEDEA quintiles and the outcomes.

Results: Compared to the least deprived, the most deprived areas were younger (43.29 (17.59) vs 46.83 (18.49), years (Mean SD), had fewer women (49.1% vs 54.8%), a higher percentage of obese (16.2% vs 8.4%), smokers (16.9% vs 11.9%) and high-risk alcohol consumption subjects (1.5% vs 1.3%). Compared to the least deprived, the most deprived areas had an excess risk of OA: age-sex-adjusted Incidence Rate Ratio (IRR) 1.26 (1.11–1.42) for hand, 1.23 (1.17–1.29) hip, and 1.51 (1.45–1.57) knee. Adjustment for obesity attenuated this association: 1.06 (0.93–1.20), 1.04 (0.99–1.09), and 1.23 (1.19–1.28) respectively.

Conclusions: Deprived areas have higher rates OA (hand, hip, knee). Their increased prevalence of obesity accounts for a 50% of the excess risk of knee OA observed. Public health interventions to reduce the prevalence of obesity in this population could reduce health inequalities.

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Introduction

Due to the improvement in life expectancy and to the increasing prevalence of age-related musculoskeletal disorders, osteoarthritis (OA) has become a major challenge for the health care systems today. Direct and indirect costs of patients suffering OA outweigh those without this diagnosis and lead to loss of working life, disability and institutionalization.

There are different individual risk factors involved in the incidence and progression of OA but these fail to fully explain the great burden of this disease. Socioeconomic studies have gained importance in order to complete the identification of risk factors and profile the characteristics of the population at risk. Some of these studies have focused on the relation between pain, disability, certain occupations, the educational attainment or the income with the incidence of musculoskeletal disorders, but few are the comprehensive multilevel studies on this matter. The use of self-reported definition of arthritis, as well as the lack of information on joint/s affected, limits the generalizability of these studies.

Life-style factors, such as smoking or obesity have been also associated with lower SES. However, while obesity has been identified as an important risk factor especially for knee OA, there is no evidence that smoking increases the risk of this musculoskeletal disease.

In the last years, socio-economic studies have gained importance in order to detect and identify potential health inequities. These exist in most developed countries for most of the illnesses including musculoskeletal disorders. Neither OA nor its main consequence, which is the joint replacement surgery are evenly distributed across the SES. Still, consequences of these potential health inequities in terms of relevant health outcomes are less clear.

Understanding the role that socio-economic risk factors play in the development of OA is key for healthcare providers, commissioners and even clinicians.

The aim of this study is therefore to determine the impact of area-based measures of SES on the risk of OA and to assess the impact of lifestyle related factors such as obesity, smoking, and high-risk alcohol consumption on these associations.

Methods

Study design

We carried out a retrospective ecological study using data from the Information System for the Development of Research in Primary Care (SIDIAP).

Setting and participants

SIDIAP is a clinical database of anonymized longitudinal primary care patient records, which include information on 5.8 million people of at least 15 years old (80% of the Catalan population and 10.2% of the total population of Spain) treated in 274 primary practices by 3414 general practitioners (GP).

The main exposure considered for this study was the ecological MEDEAd index of deprivation. It was calculated using the 2001 census-based socio-economic indicators: unemployment rates, manual work, temporary work, low educational attainment and low educational attainment among young people. The construction and validation of MEDEAd has been described in detail elsewhere. Briefly, a higher MEDEAd score is indicative of higher deprivation, and appears associated with an increased mortality in urban areas of Spain.

SIDIAP was linked to the census, after harmonizing address information and assigning each individual to their census sections. The main study exposure was the MEDEAd index of deprivation score assigned to each of the census section included, based on the census data of this population.

Eligible participants included in this study where all of those registered at a primary health care center included in the SIDIAP database from first January 2009 to the thirty-first December 2012 (study period, Fig. 1).

All subjects living in rural areas were excluded (as MEDEAd has only been validated for urban populations) as well as all those who had been diagnosed of OA at the initiation of the study period.

The study carried on, until one of the following situations occurred: (1) The subject included in the study moved out of the area where the data was collected, (2) The subject died, (3) End of the follow up period.

Variables

The information recorded includes demographic information, clinical diagnoses, events (International Classification of Diseases Tenth Revision [ICD–10]), referrals, laboratory tests and treatments (drug dispensed in community pharmacies). The quality of these data has been previously documented, and SIDIAP has been widely used to study the epidemiology of a number of health outcomes including OA and osteoporotic fractures.

Study outcomes

The study outcomes were the incident cases of: (1) hand, (2) hip, and (3) knee OA in the period 2009–2012, as recorded in the primary health care records. The ICD-10 codes used to ascertain these diagnoses have been validated elsewhere and were as follows: M15.1, M15.2, M18, and M18.0–M18.9 for hand OA; M16 and M16.0–M16.9 for hip OA; and M17 and M17.0–M17.9 for knee OA.

Confounders and potential explanatory variables

Covariates were defined a priori and adjusted for, in multivariable regression models, to explore either confounding or potential causal pathways.

Age and gender distribution and percentage of people with the characteristic of interest (current smoking, high-risk alcohol consumption (Quantity of alcohol units as a screening test of heavy drinkers in primary care), obesity as BMI of at least 30 kg/m2, percentage of people with diabetes or hypertension) were characterized at baseline (1/1/2009) at a census section level according to primary care computerized records.

Statistical analysis

MEDEAd deprivation scores were categorized into quintiles. Age and sex-standardized incidence rates were calculated for each of the study outcomes according to MEDEAd quintile.

The association between MEDEAd quintiles (the higher, the more deprived) and the incidence of these outcomes in 2009–2012 was evaluated using age and sex-adjusted zero-inflated Poisson regression. The aggregated nature of the data resulted in a higher incidence of zeros than expected if the data were Poisson distributed. Thus, the association between MEDEAd quintile (the higher, the more deprived) and the incidence of OA was evaluated using age and sex-adjusted, zero-inflated, Poisson regression modelling (Incidence Rate Ratio [IRR] and 95% CI). We further adjusted for lifestyle factors (smoking, heavy drinking, obesity) and finally fitted a multivariable model, adjusted for all these factors and for...
common comorbidities (hypertension, diabetes) to study potential causal pathways. Sex and age were included as covariates in both models for hip fracture, as well as in the modeling of excess of zeros. Smoking and obesity were also predictors of excess of zeros and hence, included in the inflation part of the model. In addition, a clustered “sandwich" estimator was calculated to estimate the variance-covariance matrix, which allowed us to account for the correlation between individuals living in the same census tract27. All the analyses were carried out using STATA v12 for Windows.

Ethical approval

Ethical approval was not required (anonymised, retrospective data).

Patient consent

Patient consent was not required (anonymised retrospective data). This study was carried out with the approval of the SIDIAP scientific committee.

Results

Cohort characteristics

Baseline characteristics are shown in Table I, A total of 3,588,807 subjects were analyzed. Compared to the least deprived, the most deprived were younger and had a lower proportion of women. In addition, they had a higher prevalence of smokers (11.9% in first quintile compared to 16.9% in fifth quintile), high-risk alcohol consumers (0.9% compared to 1.5%), and obese people (8.4% in the first compared to 16.2% in the fifth quintile).

As expected among the least deprived areas all SES measures were more frequently reported among the most deprived districts especially the proportion of manual workers (73.4% in the fifth quintile compared to 28.4% in the first quintile) and the lower educational attainment (51.6% in the fifth quintile compared to 35.9% in the first quintile).

Outcome data: incidence of OA

Incidence of hip, hand and knee OA among the different area-based levels of socioeconomic deprivation are shown in Table II, all rates are per 10,000 persons year. Knee OA was the commonest event, and it ranged from an age-sex-adjusted incidence rate of 133.3/10,000 person-years (95% CI 130.6–136.1) among the least deprived areas to 206.7 (95% CI 203.2–210.1) in the most deprived ones. Similarly, rates of hand and hip OA increased from 12.6 (95% CI 11.8–13.5) and 63.4 (95% CI 61.5–65.3) to 16.4 (95% CI 15.4–17.4) and 75.9 (95% CI 73.8–78.0) respectively.

Main results: association of SES with OA

A direct association was observed between socio-economic deprived quintiles and the risk of OA at all three sites. The unadjusted IRR for the most deprived (fifth quintile) compared to the least deprived (first quintile) was 1.29 (95% CI 1.14–1.46) for hand OA, 1.18 (95% CI 1.11–1.25) for hip OA, and 1.48 (95% CI 1.40–1.56)
for knee OA. Adjustment for age and gender was also statistically non-significant. Conversely, the observed associations between the area-based SES measures and OA at all three sites were attenuated after adjustment for the prevalence of obesity: IRR 1.06 (95% CI 0.93–1.20), 1.04 (95% CI 0.99–1.09), and 1.23 (95% CI 1.19–1.28) for hand, hip, and knee OA, respectively.

Further adjustment for smoking and high-risk alcohol consumption did not make a difference. Detailed results are reported in Tables III–V.

Discussion

Main findings

The main finding of the present study is the higher incidence of OA among our most deprived areas. Even after accounting for differences in age and gender composition, residents in these areas had a 50% excess risk of knee OA, and about a 25% higher risk of hand and hip OA when compared to the population living in the least deprived areas. A higher proportion of obese people residing in deprived areas would partially explain this association: in our data, the described relationship between deprivation and hand/hip OA was attenuated and no longer statistically significant after adjustment for the prevalence of obesity. Similarly, the effect size of the association between poor socio-economic status (SES) (with area-based measures) and risk of knee OA was halved after adjustment for obesity. Conversely, although the prevalence of smoking and high-risk alcohol consumption was higher among the population living in the deprived districts, adjustment for these variables did not alter the aforementioned associations.

Strengths and limitations

To our knowledge, this is the first study that associates SES, obesity, and risk for the development of OA using patient longitudinal data. Another strength is its large study population, which has been previously validated allowing us to easily extrapolate our results. Limitations of this study include the lack of individual based information (since the MEDEA deprivation index provides regional information), the lack of laterality of the joint affected and the urban setting where the data is gathered, not being able to determine if these results would apply to a rural area. Also, study

Table I

Baseline characteristics for study participants according to SES

<table>
<thead>
<tr>
<th>MEDEA quintiles</th>
<th>Women (%)</th>
<th>Age in years mean (SD)</th>
<th>Current smokers (%)</th>
<th>High alcohol consumption (%)</th>
<th>Obesity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>52.0</td>
<td>45.31 (18.09)</td>
<td>14.8</td>
<td>1.3</td>
<td>13.1</td>
</tr>
<tr>
<td>MEDEA quintiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>54.8</td>
<td>46.83 (18.49)</td>
<td>11.9</td>
<td>0.9</td>
<td>8.4</td>
</tr>
<tr>
<td>2</td>
<td>52.9</td>
<td>46.20 (18.33)</td>
<td>14.0</td>
<td>1.2</td>
<td>11.6</td>
</tr>
<tr>
<td>3</td>
<td>52.0</td>
<td>45.36 (18.20)</td>
<td>15.1</td>
<td>1.3</td>
<td>13.4</td>
</tr>
<tr>
<td>4</td>
<td>51.1</td>
<td>44.68 (17.82)</td>
<td>15.9</td>
<td>1.4</td>
<td>15.1</td>
</tr>
<tr>
<td>5</td>
<td>49.1</td>
<td>43.29 (17.59)</td>
<td>16.9</td>
<td>1.5</td>
<td>16.2</td>
</tr>
</tbody>
</table>

* MEDEA = 1 least deprived; MEDEA = 5 Most deprived. All P-values <0.0001.

Table II

Incidence of hand, hip, and knee OA according to SES

<table>
<thead>
<tr>
<th>MEDEA quintiles</th>
<th>Events</th>
<th>Total person-years at risk</th>
<th>Crude incidence</th>
<th>Sex-age-adjusted incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1,152</td>
<td>740,879</td>
<td>15.54 (14.61–16.48)</td>
<td>15.04 (14.18–15.91)</td>
</tr>
<tr>
<td>3</td>
<td>1,134</td>
<td>759,995</td>
<td>15.80 (14.91–16.70)</td>
<td>15.61 (14.77–16.46)</td>
</tr>
<tr>
<td>4</td>
<td>1,079</td>
<td>732,889</td>
<td>14.72 (13.80–15.64)</td>
<td>15.13 (14.25–16.01)</td>
</tr>
<tr>
<td>5</td>
<td>421</td>
<td>628,467</td>
<td>67.03 (64.84–69.22)</td>
<td>63.36 (61.45–65.26)</td>
</tr>
<tr>
<td>Hip OA</td>
<td>523</td>
<td>736,317</td>
<td>71.12 (69.00–73.24)</td>
<td>69.38 (67.52–71.25)</td>
</tr>
<tr>
<td>1</td>
<td>6052</td>
<td>822,643</td>
<td>73.56 (71.50–75.62)</td>
<td>72.66 (70.84-74.47)</td>
</tr>
<tr>
<td>2</td>
<td>5532</td>
<td>755,545</td>
<td>73.21 (71.07–75.35)</td>
<td>73.66 (71.73–75.58)</td>
</tr>
<tr>
<td>3</td>
<td>5043</td>
<td>728,478</td>
<td>69.22 (67.09–71.25)</td>
<td>75.90 (73.82–77.98)</td>
</tr>
<tr>
<td>Knee OA</td>
<td>8904</td>
<td>619,366</td>
<td>143.76 (140.24–147.27)</td>
<td>133.34 (130.61–136.07)</td>
</tr>
<tr>
<td>1</td>
<td>11,830</td>
<td>722,105</td>
<td>163.82 (160.17–167.47)</td>
<td>158.74 (155.94–161.54)</td>
</tr>
<tr>
<td>2</td>
<td>14,226</td>
<td>803,873</td>
<td>176.96 (173.26–180.67)</td>
<td>174.92 (172.11–177.73)</td>
</tr>
<tr>
<td>3</td>
<td>13,881</td>
<td>736,700</td>
<td>188.42 (184.45–192.38)</td>
<td>190.87 (187.77–193.96)</td>
</tr>
<tr>
<td>4</td>
<td>13,160</td>
<td>710,597</td>
<td>185.19 (181.16–189.22)</td>
<td>206.67 (203.22–210.12)</td>
</tr>
</tbody>
</table>

* Per 10,000 persons/year.
† MEDEA = 1 Least deprived; MEDEA = 5 Most deprived.

Table III

Results of regression models on the association between MEDEA and rates of hand OA

<table>
<thead>
<tr>
<th>MEDEA quintiles</th>
<th>Crude IRR</th>
<th>Sex-age adjusted IRR</th>
<th>Sex-age-obesity adjusted IRR</th>
<th>Life-style adjusted IRR</th>
<th>Fully adjusted IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand OA</td>
<td>1</td>
<td>1.19 (1.07–1.33)</td>
<td>1.19 (1.07–1.32)</td>
<td>1.12 (1.01–1.25)</td>
<td>1.12 (1.01–1.25)</td>
</tr>
<tr>
<td>2</td>
<td>1.23 (1.10–1.37)</td>
<td>1.21 (1.09–1.35)</td>
<td>1.10 (0.99–1.22)</td>
<td>1.10 (0.99–1.22)</td>
<td>1.09 (0.98–1.22)</td>
</tr>
<tr>
<td>3</td>
<td>1.19 (1.06–1.34)</td>
<td>1.16 (1.04–1.31)</td>
<td>1.02 (0.91–1.15)</td>
<td>1.02 (0.91–1.15)</td>
<td>1.01 (0.90–1.14)</td>
</tr>
<tr>
<td>4</td>
<td>1.29 (1.14–1.46)</td>
<td>1.26 (1.11–1.42)</td>
<td>1.06 (0.93–1.20)</td>
<td>1.06 (0.93–1.20)</td>
<td>1.05 (0.92–1.19)</td>
</tr>
</tbody>
</table>

* Previous model plus smoking, high-risk alcohol consumption.
† Previous model plus Diabetes and Hypertension.
‡ MEDEA = 1 Least deprived; MEDEA = 5 Most deprived.
events (incident OA) have not been validated for this study, but previous reports have suggested that OA recording in SIDIAP data is accurate\textsuperscript{24,25}. Furthermore, the information of the MEDEA deprivation index was based on the 2001 census and it cannot be excluded a possible variation of the SES in later years. Finally, these results might be not translatable to other countries or geographical areas.

Comparison with other studies

The association between SES and OA has been described in previous studies\textsuperscript{5,7,10,11}, most of them centered on individual SES risk factors. Our deprived areas accounted for an excess of 32% and 45% of lower educational attainment and manual workers respectively compared to the wealthy areas. Lower educational attainment that could lead to a reduced health literacy and to limitations in order to find health promoting activities\textsuperscript{7}, with the subsequent risk of obesity contributing to OA incidence\textsuperscript{26}, and the excessive load suffered by weight bearing joints\textsuperscript{9} are some of the mechanisms that could explain the higher incidence rates of OA in all three sites among lower SES.

Among the socioeconomic studies reporting an association between SES and OA, only one referred an association between BMI and the occupational activity and only two\textsuperscript{7,14} succeeded in carrying out an approach similar to the MEDEA deprivation index. Our results support all this previous data on an increased risk of OA across all deprivation levels. Public health interventions to reduce the prevalence of obesity and in consequence to an increased risk in OA.

Mechanisms through which low SES, obesity and OA interact could be also explained by environmental factors. Low physical activity, mediated through a lower presence of exercise facilities in the disadvantaged neighborhoods\textsuperscript{35} or a poorer compliance with healthy food recommendations\textsuperscript{34} could lead to the increased prevalence of obesity and in consequence to an increased risk in OA. Furthermore, differences in the delivery of healthcare depending on the social status\textsuperscript{20} could contribute to health inequities concerning OA and obesity explaining the greater prevalence of OA in our most deprived areas.

Conclusion and policy implications

In conclusion, our most deprived areas are at an increased risk of knee, hand and hip OA. OA is a progressive and disabling disease whose impact is often minimized because of its age-related nature. Its consequences affect the individual and social sphere with important loss of quality of life, loss of years of working life and increased direct and indirect health care costs\textsuperscript{35}. Our results underline the importance of obesity in the incidence of OA among the most deprived. Public health interventions to reduce the

Table IV

<table>
<thead>
<tr>
<th>MEDEA quintiles</th>
<th>Crude IRR</th>
<th>Sex-age adjusted IRR</th>
<th>Sex-age-obesity adjusted IRR</th>
<th>Life-style adjusted IRR\textsuperscript{5}</th>
<th>Fully adjusted IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee OA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.15 (1.05–1.25)</td>
<td>1.19 (1.14–1.23)</td>
<td>1.10 (1.06–1.14)</td>
<td>1.10 (1.06–1.14)</td>
<td>1.10 (1.06–1.14)</td>
</tr>
<tr>
<td>3</td>
<td>1.30 (1.24–1.36)</td>
<td>1.30 (1.25–1.35)</td>
<td>1.15 (1.11–1.19)</td>
<td>1.16 (1.11–1.20)</td>
<td>1.15 (1.11–1.19)</td>
</tr>
<tr>
<td>4</td>
<td>1.42 (1.35–1.49)</td>
<td>1.42 (1.36–1.47)</td>
<td>1.21 (1.16–1.25)</td>
<td>1.21 (1.17–1.26)</td>
<td>1.20 (1.16–1.25)</td>
</tr>
<tr>
<td>5</td>
<td>1.48 (1.40–1.56)</td>
<td>1.51 (1.45–1.57)</td>
<td>1.23 (1.19–1.28)</td>
<td>1.24 (1.20–1.29)</td>
<td>1.23 (1.19–1.28)</td>
</tr>
</tbody>
</table>

\* Previous model plus smoking, high-risk alcohol consumption.
\# Previous model plus Diabetes and Hypertension.
\textsuperscript{5} MEDEA – 1 Least deprived; MEDEA – 5 Most deprived.

Table V

<table>
<thead>
<tr>
<th>MEDEA quintiles</th>
<th>Crude IRR</th>
<th>Sex-age adjusted IRR</th>
<th>Sex-age-obesity adjusted IRR</th>
<th>Life-style adjusted IRR\textsuperscript{5}</th>
<th>Fully adjusted IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip OA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.08 (1.03–1.14)</td>
<td>1.10 (1.05–1.16)</td>
<td>1.04 (0.99–1.09)</td>
<td>1.04 (0.99–1.09)</td>
<td>1.03 (0.98–1.08)</td>
</tr>
<tr>
<td>3</td>
<td>1.13 (1.07–1.18)</td>
<td>1.16 (1.11–1.22)</td>
<td>1.05 (1.01–1.11)</td>
<td>1.05 (1.00–1.10)</td>
<td>1.04 (0.99–1.09)</td>
</tr>
<tr>
<td>4</td>
<td>1.15 (1.09–1.21)</td>
<td>1.19 (1.14–1.25)</td>
<td>1.04 (0.99–1.09)</td>
<td>1.04 (0.99–1.09)</td>
<td>1.03 (0.98–1.08)</td>
</tr>
<tr>
<td>5</td>
<td>1.18 (1.11–1.25)</td>
<td>1.23 (1.17–1.29)</td>
<td>1.04 (0.99–1.09)</td>
<td>1.04 (0.98–1.09)</td>
<td>1.02 (0.97–1.07)</td>
</tr>
</tbody>
</table>

\* Previous model plus smoking, high-risk alcohol consumption.
\# Previous model plus Diabetes and Hypertension.
\textsuperscript{5} MEDEA – 1 Least deprived; MEDEA – 5 Most deprived.
prevalence of obesity in these populations would have the potential to reduce the risk of OA and therefore to minimize health inequalities. While this happens, healthcare resources should be improved in deprived populations, as these will be at an increased risk.

Author contributions

MGG, JME, LMB, EH: Data extraction, statistical analysis and manuscript preparation. DPA: Study design, data analysis and interpretation and manuscript preparation. CR: data interpretation and manuscript preparation. MKJ, CC, ADP, NKA: study design and manuscript preparation. BB and RR: manuscript preparation.

All authors reviewed the manuscript contents and approved it for submission.

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Conflict of interests

D.P.A has received unrestricted research grants from BIOIBERICA SA (P681566 and P687368) and AMGEN (P718688); A.D.P reports personal fees from AMGEN/GSK, personal fees from Lilly, personal fees from VitaV, personal fees from Novartis, from Merck, other from Active Life Sci, outside the submitted work; N.K.A is consultant or lecturer for Flexion, Lilly, Merck, Q-Med, Roche and Smith & Nephews, Amgen, GSK, NiCox, has received grants from Novartis, Pfizer, Sheering-Plough and Servier; M.K.J is honoraria/advisory boards from Servier, Lilly, Merck, AMGEN and Medtronic; B.B reports grants from Instituto de Salud Carlos III (PI11/01932), during the conduct of the study; grants from Sanofi, Astra-Zeneca, AMGEN, Bioiberica, Novartis, MSD, grants from RTI Health Solutions, United Biosource Corporation, IMS Health, outside the submitted work; C.R, C.C, J.M.E, M.G.G, L.M.B, E.H and R.R have no non-financial interests that may be relevant to the submitted work.

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Supplementary data

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