1   Introduction

2   Osteoarthritis (OA) is a common reason for consultation in primary care with 4% of adults

3   aged 45 years and over consulting each year for OA (Jordan et al. 2013).

4   Although traditionally viewed as a degenerative disease of joints, OA can be considered to

5   have different phenotypes of disease with distinct clinical characteristics or causal factors

6   (Bijlsma, Berenbaum & Lafeber 2011). Obesity is a risk factor for OA (Cooper et al. 1998) but

7   this may be more than a purely mechanical effect (Sellam, Berenbaum 2013). Diabetes has

8   been associated with different musculoskeletal conditions and has also been identified as a

9   risk factor for OA, independently of body mass index (BMI) (Louati et al. 2015). Conversely

10   an increased risk of type 2 diabetes in people with OA has also been identified (Rahman et

11   al. 2014). This OA phenotype has been described as an expression of the metabolic

12   syndrome (Velasquez, Katz 2010). Insulin resistance is thought to be associated with the

13   development of OA (Hamada et al. 2015).

14   Statin treatment for primary or secondary prevention of vascular disease has been found to

15   be associated with a reduction in some manifestations of clinical OA (Kadam, Blagojevic &

16   Belcher 2013). Although a causal mechanism for this association has not been established, it

17   is plausible that the relationship is due to OA forming a part of the metabolic syndrome.

18   Metformin as a treatment for type 2 diabetes has previously been investigated to determine

19   whether it is associated with a reduction in the risk of cardiovascular events and all-cause

20   mortality, but with conflicting findings (Boussageon et al. 2012).

21   There is limited knowledge about the effects of metformin on risk of OA. It has been

22   hypothesised that metformin is associated with bone health through promotion of

23 differentiation of osteoblasts and their regulation and protection from hyperglycaemia (Yan,

24 Li 2013), and metformin is considered to have beneficial effects on insulin resistance

25 (Wiernsperger, Bailey 1999).

26 We hypothesised that patients with type 2 diabetes treated with metformin may show a

27 reduced risk of OA compared to people with type 2 diabetes not so treated. To investigate

28 this, we conducted a longitudinal analysis using routinely recorded electronic health record

29 data.

30

Methods

31

Study Design and Setting

32

33 This study used a cohort design using the Consultations in Primary Care Archive (CiPCA)

34 database, an anonymised database of routinely recorded information from 13 general

35 practices in North Staffordshire, UK (Porcheret et al. 2004, Jordan et al. 2007). Practices

36 undergo regular assessment, feedback and training on the quality of their morbidity

37 recording (Porcheret et al. 2004). Prevalence of consultation for musculoskeletal conditions

38 has been shown to be similar to national and international databases (Jordan et al. 2013).

39 Practices contributing to CiPCA use the Read code system for recording morbidity as is most

40 common in UK primary care.

Study population

41

42 To be eligible, patients had to be aged 40 or over and have had either a recorded diabetes

43 diagnosis or diabetes treatment between January 2002 and December 2003 (the "baseline

44 period"). Read codes for diabetes are available from our website www.keele.ac.uk/mrr.

45   Each patient's index date was defined as the first occurrence of a diagnosis of diabetes or

46   prescription of a diabetic drug. Patients with a prior record of OA in the previous 2 years

47   were excluded, as were patients with a record of type 1 diabetes (identified either through

48   Read code or through linked consultation text). All eligible participants had a minimum of

49   one year prior registration at their practice.

50   *Exposure*

51   Prescription information was available for all participants for their time in the study and at

52   least 12 months prior to cohort entry. Those patients prescribed a drug for diabetes (BNF

53   Chapter 6.1) would typically have multiple repeat prescriptions, and may switch between

54   metformin and non-metformin treatments. A non-metformin prescription was defined as

55   any other diabetic drug, or a diet and lifestyle advice (no drug) treatment only. Two

56   approaches were conducted to investigate association of exposure to metformin with OA.

57   The first analysis compared risk of future OA diagnosis based on baseline treatment

58   (metformin prescription or not in the baseline period 2002-2003).

59   The second analysis incorporated change in pharmacological treatment of diabetes

60   (metformin versus non metformin) over time. Patients not prescribed metformin in the

61   baseline period but later prescribed metformin were deemed to be exposed to metformin

62   from the date of the first such prescription. If a patient prescribed metformin was then not

63   recorded as having a metformin prescription for 6 months at any subsequent point during

64   follow-up, metformin exposure was deemed to have ended 28 days after the last recorded

65   prescription If a prescription was recorded within 6 months of a prior prescription,

66   metformin exposure was deemed to have continued uninterrupted. This is consistent with

67 previous work within our Research Institute and with guidelines that GPs should prescribe a

68 maximum of a 28 day supply of medication per prescription.

69 *Outcome*

70 The primary outcome of interest was the first occurence of an OA diagnosis during the

71 follow-up period, defined by Read code N05 "Osteoarthritis and allied disorders" and all

72 child codes. Follow-up continued to the end of 2011, the end of patient registration at their

73 practice, end of practice records in CiPCA, or the first record of OA.

74 *Covariates*

75 Covariates considered to be potential confounders of the relationship of metformin with OA

76 diagnosis included age at index date, gender, GP practice, neighbourhood deprivation, and

77 comorbidity. Comorbidity was defined as number of different prescription drugs (based on

78 British National Formulary codes) prescribed during the baseline period and categorised into

79 4 groups; 0-5, 6-9, 10-13, and 14+, based on quartiles. This measure has been shown to be

80 an efficient measure of comorbidity for healthcare use (Perkins et al. 2004).

81 Measurement of neighbourhood deprivation was based on the Index of Multiple

82 Deprivation (IMD) 2007, a small area-level measure of deprivation across England

83 (Department for Communities and Local governments 2007). This variable was categorised

84 based on quintiles, the first category representing the most deprived in the population, and

85 the fifth category representing the least deprived.

86 *Statistical Analyses*

87 Cox proportional hazards regression models were fitted with Gamma frailty term. This is

88 essentially a random effects model to address variability in outcomes across patients (i.e.

89 different underlying frailty) related to unobserved covariates (Hougaard 1995). The shared

90 frailty term in this case assumes that the frailty is common to patients within the same

91 practice.

92 The proportional hazards assumptions were checked for both models fitted, and sensitivity

93 analyses were conducted to test the robustness of the results to the distributional

94 assumptions placed on the random effect. In place of a Gamma distribution, the commonly

95 used Gaussian frailty term was added to the model (Yashin 2001).

96 All analyses were completed using R version 3.2.2 through R studio version 0.99.473 for

97 Windows.

98

Results

100 54,006 patients aged forty and over were registered at the 13 CiPCA practices in 2002.

101 There were 4164 patients with a record of diabetes in 2002 or 2003. Of these 133 were

102 excluded due to having a record of type 1 diabetes; 98 due to having no consultation

103 information recorded during follow-up; 712 due to having a diagnosis of OA prior to their

104 start date in the study; and a further 4 were removed due to having a diagnosis of OA on

105 their index date. The remaining 3217 patients were eligible to be included in the analysis.

106 *Baseline exposure analysis*

107 Initially patients were split into treatment groups based on prescriptions received during the

108 baseline period. There were 1838 (57.13%) patients prescribed metformin, and 1379

109 (42.87%) not prescribed metformin; 13.92% of those in the non-metformin group were on

110   lifestyle and diet changes only, whilst the remaining 86.08% received a prescription for

111   another anti-diabetic drug.

112   Those prescribed metformin at baseline tended to be younger (mean age 64.08 [SD: 11.33]

113   years versus 68.64 [SD: 11.90) but were similar in terms of gender, deprivation and median

114   number of other prescription drugs during baseline (table 1).

115   Median follow-up was 8.50 (IQR: 4.08, 9.86) years for those prescribed metformin, and 7.63

116   (IQR: 2.98, 9.47) for those not prescribed metformin.

117   347 (18.88%) of those prescribed metformin had a diagnosis of OA during follow-up

118   (incidence: 301.26; 95% CI: (271.17, 334.69) per 10,000 person years); 244 (17.69%) of those

119   not prescribed metformin at baseline had a diagnosis of OA (314.55/10,000; 95% CI: 277.46,

120   356.61)).

121   There was no association of baseline prescription of metformin with OA (unadjusted HR:

122   0.97, (95% CI: 0.87, 1.10), adjusted HR: 1.02 (95% CI: 0.91, 1.15))(table 2).

123   Age (HR: 1.01 per year, (95% CI: 1.01, 1.02)), female gender (HR: 1.28, (95% CI: 1.09, 1.52)),

124   and more prescription drugs 14+ versus 0-5 (HR: 2.18, (95% CI: 1.71, 2.79)) were associated

125   with OA diagnosis during follow-up, whereas deprivation was not associated with OA

126   diagnosis. The gamma frailty term was significant, indicating significant heterogeneity

127   between GP practices.

128   One practice had only 36 registered patients in the analysis and appeared to violate the

129   proportional hazards assumption. Its removal from the analysis did not change the findings.

130   Changing the gamma frailty term to a Gaussian did not substantially change the hazard

131   ratios.

132 *Time-varying analysis*

133 2289 (71.11%) patients had a metformin prescription at some point during follow-up; 196

134 (8.56%) of these patients received a diagnosis of OA whilst they were on a metformin

135 prescription.

136 2885 (89.62%) patients had a period of follow-up when they were not prescribed

137 metformin, of which 395 (13.69%) were diagnosed with OA whilst they were on a non-

138 metformin prescription.

139 Prescription of metformin (allowing exposure to vary over time) was not associated with a

140 new OA diagnosis (unadjusted HR 0.93 (95% CI: 0.78, 1.10), adjusted HR 0.98 (95% CI: 0.82,

141 1.16). There was a similar relationship with OA for gender, age, deprivation score, and

142 number of recorded prescriptions as in the analysis conducted on the baseline data (table

143 2).

144 The addition of the random effect was again significant.

145 The proportional hazards assumption was checked and satisfied for this model. Using a

146 Gaussian rather than Gamma frailty term did not substantially change the estimated HRs.

147 ## Discussion

148 In this cohort of diabetes patients with up to 10 years of follow-up, no significant association

149 was found between prescription of metformin and diagnosis of OA.

150 Consistent with previous literature we identified an increase in risk with increasing age and

151 an increased risk for females. We also identified a dose response relationship with number

152 of other prescription drugs as a marker of comorbidity and risk of OA.

153   Diabetes has been shown to have an independent association with OA (5). This is the first

154   population-based cohort study to examine whether metformin, a common treatment for

155   diabetes, can have a protective effect against OA in those with diabetes. A major strength of

156   this project is the large sample size from a primary care population database that has been

157   found to give similar results for prevalence of musculoskeletal conditions compared to

158   national databases (Jordan et al. 2013). The findings are therefore likely to be generalisable

159   to the UK as a whole.

160   There is variability between clinicians in diagnosing and recording OA, with some preferring

161   a non-specific 'joint pain' term (Jordan et al. 2016). We have used only the OA diagnostic

162   term in this study and so may have under-ascertained cases of OA but are likely to have

163   included patients with more severe joint pain (Jordan et al. 2007).

164   27.2% patients had no recorded type associated with a diabetes diagnosis but were

165   assumed to have type 2. This may be have led to a degree of misclassification but there is no

166   reason to believe this should have biased the results. We did not assess OA in specific joints.

167   Since the metabolic phenotype of OA has been suggested to predominantly affect the hand,

168   knee, and generalised OA (Bijlsma, Berenbaum & Lafeber 2011), further work to examine

169   the effect of metformin on site-specific OA would be appropriate. Patients may have had a

170   previous diagnosis of OA more than 2 years before the index date, and so in some cases we

171   may have identified new consulting episodes of OA rather than first ever diagnosis.

172   Although the estimated association between metformin and OA was adjusted for potential

173   confounders such as age and gender, we lacked information for this analysis about other

174   pertinent covariates such as BMI. As the prescription of metformin in clinical practice is

175   linked to increased BMI, the lack of adjustment for BMI may hide any association of

176   metformin with reduced risk of OA .

177   Similarly any effect of metformin may plausibly be linked to dosage and duration which we

178   have not investigated here.

179   In conclusion, this study has not identified evidence of an association of metformin with OA

180   but further research should assess the effects of dosage and duration on treatment,

181   incorporate BMI, and ascertain associations with site-specific OA.

182 Ethics approval

185 Acknowledgements

188 Financial Support

Conflict of Interest

The authors have declared no conflicts of interest.

References

Bijlsma, J., Berenbaum, F. & Lafeber, F. 2011, "Osteoarthritis: an update with relevance for clinical practice.", *The Lancet,* vol. 377, no. 9783, pp. 2115-2126.

Boussageon, R., Supper, I., Bejan-Angoulvant, T. & et al. 2012, "Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials.", *PLoS medicine,* vol. 9, no. 4, pp. e1001204.

Cooper, C., Inskip, H., Croft, P. & et al 1998, "Individual Risk factors for Hip Osteoarthritis: Obesity, Hip Injury and Physical Activity.", *Am J Epidemiol,* vol. 147, no. 6, pp. 516-522.

Department for Communities and Local governments 2007, *, English Indices of Deprivation 2010* [Homepage of UK Gov], [Online]. Available: http://data.gov.uk/dataset/index-of-multiple-deprivation [2015, 06].

Hamada, D., Maynard, R., Schott, E. & et al. 2015, "Insulin Suppresses TNF-dependent Early Osteoarthritic Changes Associated with Obesity and Type 2 Diabetes.", *Arthritis & Rheumatology,* .

Hougaard, P. 1995, "Frailty models for survival data", *Lifetime Data Analysis,* vol. 1, no. 3, pp. 255-273.

Jordan, K.P., Tan, V., Edwards, J.J., Chen, Y., Englund, M., Hubertsson, J., Jöud, A., Porcheret, M., Turkiewicz, A. & Peat, G. 2016, "Influences on the decision to use an osteoarthritis diagnosis in primary care: a cohort study with linked survey and electronic health record data, Osteoarthritis and Cartilage", *Osteoarthritis and Catrilage,* .

Jordan, K., Clarke, A., Symmons, D., Fleming, D., Porcheret, M., Kadam, U. & Croft, P. 2007, "Measuring disease prevalence: a comparison of musculoskeletal disease using four general practice consultation databases.", *British Journal of General Practice,* vol. 57, pp. 7-14.

Jordan, K., Jöud, A., Bergknut, C., Croft, P., Edwards, J., Peat, G., Petersson, I., Turkiewicz, A., Wilkie, R. & Englund, M. 2013, "International comarisons of the consultation prevalence of musculoskeletal conditions using population-based health care data from England and Sweden", *Ahn Rheum Dis.,* vol. 73, no. 1, pp. 212-218.

Kadam, U., Blagojevic, M. & Belcher, J. 2013, "Statin use and clinical osteoarthritis in the general population: a longitudinal study", *Journal of general internal medicine,* vol. 28, no. 7, pp. 943-949.

Louati, K., Vidal, C., Berenbaum, F. & Sellam, J. 2015, "Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis", *Rheumatic and Muskuloskeletal Diseasers,* vol. 1, no. 1.

231   Perkins, A., Kroenke, K., Untzer, J., Katon, W., Williams, J. & Hope, C. 2004, "Common
232   comorbidity scales were similar in their ability to predict health care costs and
233   mortality.", *Journal of Clinical Epidemiology,* vol. 57, no. 10, pp. 1040-1048.

234   Porcheret, M., Hughes, R., Evans, D., Jordan, K., Whitehurst, T., Ogden, H., Croft, P. & North
235   Staffordshire General Practice Research Network. 2004, "Data Quality of General
236   Practice Electronic Health Records: The Impact of a Program of Assessments, Feedback,
237   and Training", *Journal of the American Medical Informatics Association,* vol. 11, no. 1,
238   pp. 78-86.

239   Rahman, M., Cibere, J., Anis, A. & et al. 2014, "Risk of Type 2 Diabetes among Osteoarthritis
240   Patients in a Prospective Longitudinal Study.", *International Journal of Rheumatology,*
241   vol. 2014, no. 7.

242   Sellam, J. & Berenbaum, F. 2013, "Is osteoarthritis a metabolic disease?", *Joint Bone Spine,*
243   vol. 80, pp. 568-573.

244   Velasquez, M. & Katz, J. 2010, "Osteoarthritis: another component of metabolic
245   syndrome?", *Metabolic syndrome and related disorders,* vol. 8, no. 4, pp. 295-305.

246   Wiernsperger, N.F. & Bailey, C.J. 1999, "The antihyperglycaemic effect of metformin:
247   therapeutic and cellular mechanisms.", *Drugs,* vol. 1, no. 6, pp. 31-39.

248   Yan, W. & Li, X. 2013, " Impact of diabetes and its treatments on skeletal diseases.", *Front
249   Med,* vol. 7, no. 1, pp. 81-90.

250   Yashin, A.I. 2001, *Hidden frailty: myths and reality*, Department of Statistics and
251   Demography, Odense University.

252