Prevalent Rheumatoid Arthritis and Diabetes Among NHANES III Participants Aged 60 and Older

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ABSTRACT. Objective. This study examines the cross-sectional association between prevalent rheumatoid arthritis (RA) and diabetes among noninstitutionalized US civilians aged ≥ 60 years between 1988 and 1994.

Methods. Using National Health and Nutrition Examination Survey III data from the National Center for Health Statistics, RA and diabetes were identified using several classification schemes. In total, 5302 survey participants aged ≥ 60 years were included in logistic regression analyses taking survey weights into account. We also conducted sensitivity analyses restricting the study population to participants not recently prescribed glucocorticoids and fasting at least 8 hours prior to blood draw, as well as data incorporated from the Multiple Imputation Project.

Results. Among the 5302 participants aged ≥ 60, 144 participants had RA and 24 of these also were found to have prevalent diabetes. The adjusted odds ratios for the cross-sectional association between RA and diabetes ranged from 1.1 to 1.5, but did not reach statistical significance.

Conclusion. While this study cannot definitively rule out a modest non-null association, we can conclude that there is no evidence of a strong cross-sectional association between prevalent RA and diabetes in subjects aged ≥ 60 years. Future longitudinal studies with more participants with RA are required to further evaluate a possible association between RA and the incidence of diabetes.

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Key Indexing Terms:
RHEUMATOID ARTHRITIS      DIABETES      OLDER PERSONS
NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY III

Chronic inflammatory diseases, such as rheumatoid arthritis (RA), lead to increases in systemic markers of inflammation such as C-reactive protein (CRP) and interleukin 6 (IL-6), which have been shown to be associated with the incidence of diabetes mellitus (DM)1-8. Some9,10 but not all11-13 previous studies have shown an association between RA and diabetes. However, none was specifically designed a priori to test this association, and the statistical analyses presented in these publications did not adequately control for potential confounding.

Several studies have demonstrated positive associations between systemic markers of inflammation and type 2 diabetes1,2,14-16. For example, in a prospective cohort study, Schmidt and colleagues found that high white blood cell count was associated with increased risk of diabetes, with a statistically significant odds ratio of 1.9 (95% CI 1.6–2.3) after adjustment for potential confounders in multivariable models15. Their finding was robust in sensitivity analyses varying their working definition of diabetes. Pickup, et al demonstrated that among Caucasian clinic patients of European origin with diabetes, patients with metabolic syndrome had higher levels of inflammatory markers including CRP and IL-614.

We used nationally representative data from the National Health and Nutrition Examination Survey (1988 to 1994) (NHANES III) to investigate the cross-sectional association between prevalent RA and DM after controlling for potential confounding factors among subjects aged 60 years and over who underwent upper extremity examinations.

MATERIALS AND METHODS

NHANES III was a cross-sectional survey conducted between 1988 and 1994 by the National Center for Health Statistics (NCHS) at the US Centers for Disease Control (Bethesda, MD, USA). The survey included a probability sample representative of the noninstitutionalized US civilian population. Sample weights were used to generate population estimates by adjusting for differential selection probabilities due to oversampling of Black Americans and Mexican Americans, noncoverage, and nonresponse. NHANES III surveyed and examined 39,695 participants aged 2 months and older, without specifying an upper age limit. Data were collected from a series of home interviews, medical examinations, and laboratory procedures. Physical examination of the upper extremities was performed only on participants aged ≥ 60 years who attended the medical examination center.

Study population. Of 39,695 NHANES III participants, 86% (n = 33,994) participated in the home interview, and of those, 6596 participants were aged ≥ 60 years. Included in our analysis are a total of 5302 (80%) of these older, interviewed participants who were examined at the medical examination center, where their upper extremities, knees, and great toe joints were evaluated for joint swelling and tenderness; the presence of subcutaneous nodules was also recorded.

Definition of RA. Because self-report of RA is known to be poorly associated with presence of confirmed RA, we used the classification scheme proposed...
by Rasch, et al\textsuperscript{17} to identify participants with RA within NHANES III. Given the cross-sectional design of the NHANES III data, the American College of Rheumatology (ACR) criteria\textsuperscript{18} were modified by Rasch, et al\textsuperscript{17} to facilitate the classification of prevalent RA cases in the presence of appropriate interview and examination data.

For our primary analyses, we classified participants as having RA if they fulfilled the definition of RA by Rasch and colleagues’ method \textsuperscript{3} (n = 144). In this method, subjects were evaluated according to the classification tree algorithm described by Arnett, et al\textsuperscript{18}. This approach allows the use of surrogate classification variables when a primary variable is not available. In this instance, Rasch, et al\textsuperscript{17} made 2 modifications to the ACR criteria. Because there were no anteroposterior radiographs of the hands and wrists evaluated for the presence of RA, Rasch, et al\textsuperscript{17} substituted the presence of metacarpophalangeal swelling on examination for this criterion. In addition, for those subjects that had missing data for rheumatoid factor (RF) titers, Rasch and colleagues’ algorithm substituted this criterion for the presence of wrist swelling on examination. Subjects were classified as having RA if they met any 3 of these revised ACR criteria or if they self-reported RA and were using disease modifying antirheumatic drugs (DMARD). Additionally, subjects who were taking DMARD and met at least one ACR criterion were considered to have RA even if they did not self-report. Self-reported disease was recorded by subjects’ response to the questions, “Has a doctor ever told you that you had arthritis?” and “Which type of arthritis was it? Was it rheumatoid arthritis or osteoarthritis?”

We conducted additional analyses using 2 alternative definitions of RA as described by Rasch, et al\textsuperscript{17}. In our alternative definition 1 (corresponding to Rasch’s method 1), we classified participants as having RA if they met any 3 traditional ACR criteria (n = 131). In our alternative definition 2 (corresponding to Rasch’s method 2), we applied the classification tree algorithm using surrogates as described above (n = 132)\textsuperscript{18}.

**Definition of diabetes.** Subjects were classified as having diabetes if they answered yes to any one of the following questions: “Have you ever been told you have sugar diabetes?” “Are you now taking insulin?” or “Are you now taking diabetes pills?” In addition, subjects who reported taking a prescription medication with a corresponding International Classification of Disease-9 code of 250.0 (diabetes without mention of complication, type 2) or 250.9 (diabetes with unspecified complication) were also considered to have diabetes. Female participants reporting only gestational diabetes were not classified as having diabetes in this study. Six participants had inadequate data to classify their diabetes status and were removed from the analysis. We also conducted a set of sensitivity analyses in which we restricted the population to participants who had fasted at least 8 hours prior to their blood draw. In these analyses, we classified participants as having diabetes if they fulfilled the criteria above or if their fasting plasma glucose was > 125 mg/dl\textsuperscript{19}.

**Additional covariates.** Blood pressure was defined as the average of the second and third systolic and diastolic readings\textsuperscript{20}. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m\textsuperscript{2}), using medical examination measurements. Latex-enhanced nephelometry was used to measure serum CRP and RF. RF screening used the 2-channel, 2-value Behring Nephelometer analyzer system (Behring Diagnostics) and titration determined manually by the Singer-Plotz latex agglutination procedure. All nonzero RF values were considered positive. High density lipoprotein (HDL)-cholesterol was measured after precipitation from a heparin-manganese chloride mixture. Low density lipoprotein (LDL)-cholesterol was derived mathematically from the known relationship between LDL, very low density lipoprotein, HDL, and total cholesterol. The Cobas Mira assay was used for the enzymatic reaction to measure plasma glucose\textsuperscript{21}.

Individuals were asked whether they participated in a variety of activities in the past month including jogging, biking, swimming, gardening, and weight lifting. Additional open-ended questions and probes were included in the interview to account for activities not defined in the interview (“In the past month have you done any other exercises, sports, or physically active hobbies not mentioned?”). Individuals were considered physically inactive if they participated in none of these activities in the past month. Participants were classified as having never smoked if they smoked < 100 cigarettes in their lifetime, past smokers if they smoked at least 100 cigarettes in their life but did not currently smoke, or current smokers. Educational attainment was classified as less than high school (eighth grade and below), some high school, high school graduate, and some college.

Participants were asked, “Have you taken or used any medicines for which a doctor’s or dentist’s prescription is needed, in the past month?” For any affirmative response subjects were asked to show the medication bottle to the interviewer, and if unavailable, the interviewer probed for further details. Each identified medication was entered as a standard 4-digit code from the Physician’s GenRx. Subjects reported the following DMARD: auranofin (n = 1), methotrexate sodium (n = 7), azathioprine (n = 1), penicillamine (n = 2), sulfasalazine (n = 7), and hydroxychloroquine sulfate (n = 5). Compared to Rasch and colleagues’ classification\textsuperscript{17}, our study identified an additional subject using DMARD after incorporating updated data from NHANES released errata files\textsuperscript{22}. Among NHANES III participants aged ≥ 60 years, methylprednisolone (n = 3), prednisone (n = 80), prednisolone (n = 1), and triamcinolone (n = 3) were reported as prescribed glucocorticoids. Indicator variables were created for use of any DMARD and any glucocorticoids.

**Statistical analysis.** Differences in covariate distributions between those with RA and those free of disease were compared using Wald and Pearson tests taking survey weights into account\textsuperscript{23}, for continuous and categorical variables, respectively. The survey weights used are those for the medical examination center over the entire 6 year follow-up (NHANES III variable name: wtfx6). Continuous variables were log-transformed if needed to achieve normality prior to testing the differences in means. Logistic regression models taking these survey weights into account were fit to assess the association between prevalent RA and the outcome, diabetes. Covariates believed to be potential risk factors for both RA and DM were adjusted for in the analysis to control for confounding; these included age, sex, race/ethnicity, education, and smoking. Further analyses were performed adjusting for covariates believed to be intermediates on a hypothesized pathway between RA and diabetes, including physical inactivity, BMI, and glucocorticoid prescription. Additionally, a sensitivity analysis was performed restricting to subjects not recently prescribed glucocorticoids and fasting at least 8 hours prior to blood draw. Further, we incorporated data released from the NHANES III Multiple Imputation Project allowing for modest increases in power by including imputed data relevant to this study such as weight, height, poverty level, glucose, and fasting status at blood draw.

Data management was performed using SAS v9.1, while all analyses used Stata v8.0 software to account for the complex sampling techniques used in NHANES survey samples. Sample weights were calculated using Statistical Innovation’s Chi-Square Automatic Interaction Detection (SI-CHAID) software and provided by NCHS in the data file to account for sampling methods (such as oversampling), nonresponse bias, and noncoverage\textsuperscript{24}.

**RESULTS**

Table 1 shows that persons with RA tended to be older and more likely to be female and physically inactive compared to participants free of RA. However, there were no differences in smoking status, BMI, plasma glucose, or lipids. NHANES III participants with RA tended to be less likely to have graduated from high school. As expected, individuals with RA were more likely to experience morning stiffness, use DMARD and corticosteroids, and have positive RF and elevated CRP compared to persons free of disease.

Among the 144 participants with RA there were 24 who also had prevalent diabetes (17%) compared with 16% (n = 815) of the 5152 participants without RA (p = 0.46). In a logistic regression model controlling for age and sex the odds ratio for the RA-diabetes association was 1.3 (95% CI 0.68–2.3). The association was not altered after multivariable adjustment also controlling for race, smoking, and education...
The association was also not altered in a set of models adjusting for factors that may be on a causal pathway between RA and diabetes should such an association exist, including BMI, steroid use, physical inactivity, and socioeconomic status. Further, the association was also not altered when repeated using the 2 alternative classifications of RA described above. The sensitivity analyses incorporating the NHANES released imputed data, restricting to those fasting at least 8 hours prior to blood draw, and incorporating plasma glucose measures into the definition of diabetes yielded consistently weak, positive effect estimates with wide confidence intervals (Table 3). Of the nearly 3000 participants included in these sensitivity analyses, 89 subjects were identified as having RA, 18 of whom also had prevalent diabetes.

**DISCUSSION**

In this study of NHANES III participants aged ≥ 60 years who attended the medical examination center, there was no statistically significant association between prevalent RA and DM. Neither age and sex adjusted models nor multivariable analysis showed a significant non-null cross-sectional association. Sensitivity analyses restricting to persons not currently...
using glucocorticoids, fasting at blood draw, and refining the definition of diabetes showed consistently weak positive associations with relatively wide confidence intervals that did not reach statistical significance for any of the 3 definitions of RA described by Rasch, et al.

**Inflammation, diabetes, and RA.** The chronic inflammation in RA has been shown to lead to increased levels of CRP and IL-6. The resultant inflammatory state may in turn lead to an increased risk of diabetes among patients with RA. Chronic inflammation has been identified as a risk factor for DM. For example, in a prospective, nested case-control analysis within the Women’s Health Study, Pradhan and colleagues found that inflammatory markers such as CRP and IL-6 predicted the occurrence of type 2 diabetes. In the prospective Cardiovascular Health Study of subjects aged ≥ 65 years, Barzilay and colleagues reported a significantly increased risk of diabetes associated with higher CRP levels. The multivariable adjusted odds ratio comparing subjects in the highest quartile (≥ 0.286 mg/dl) to those in the lowest quartile (< 0.082 mg/dl) was 1.83 (95% CI 1.24–2.86).

Two studies have suggested an association between RA and diabetes. Del Rincon and colleagues, studying the association between RA and incident fatal and nonfatal cardiovascular events, reported a statistically significant crude association between ACR-defined RA and prevalent diabetes. However, the association could be entirely explained by differences in age between the subjects with RA and those participants free of this disease. Dessein and colleagues considered numerous outcomes and comorbidities among patients with RA compared to patients with osteoarthritis. They found a higher frequency of type 2 diabetes among patients with RA (10%; 8/79) compared to those with osteoarthritis (3%; 1/37) that did not reach statistical significance (p = 0.27). However, a multivariable analysis of this association was not presented.

**Limitations.** Our study has several limitations. First, the cross-sectional design restricts the analysis to an association between 2 prevalent diseases and cannot address disease incidence, temporality, or causality. The prevalence of both RA and diabetes depends upon disease incidence and duration. In effect, the NHANES III participants aged ≥ 60 years represent a population of survivors. If there were a higher mortality rate among people with both RA and DM than would be expected based on the mortality rates among individuals with either condition alone, then the number of subjects with both conditions surviving to be included in the NHANES III population would underestimate the true concurrence of these conditions. While this point may not be of importance to consider the burden of disease at a given point in time, it may prohibit understanding the extent of the association between RA and DM.

In our study, adjusting for potential intermediate variables such as BMI, physical inactivity, low socioeconomic status, and medication use did not alter the estimated odds ratios appreciably. We accounted for glucocorticoids in 2 ways. In one set of analyses, we included an indicator variable in our

### Table 2. Association between prevalent RA and diabetes in NHANES III subjects aged 60 and older (n = 5296).

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Classification</td>
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<tr>
<td>Unadjusted</td>
<td>1.3 (0.68–2.3)</td>
<td>0.46</td>
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<td>Age and sex adjusted*</td>
<td>1.3 (0.68–2.4)</td>
<td>0.47</td>
</tr>
<tr>
<td>Multivariable adjusted**</td>
<td>1.3 (0.67–2.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Further adjusted ***</td>
<td>1.3 (0.64–2.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Alternative classification 1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.1 (0.59–2.2)</td>
<td>0.69</td>
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<tr>
<td>Age and sex adjusted*</td>
<td>1.1 (0.58–2.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Multivariable adjusted**</td>
<td>1.1 (0.58–2.2)</td>
<td>0.70</td>
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<tr>
<td>Further adjusted ***</td>
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<tr>
<td>Alternative classification 2††</td>
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<tr>
<td>Age and sex adjusted*</td>
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<tr>
<td>Multivariable adjusted**</td>
<td>1.3 (0.66–2.5)</td>
<td>0.44</td>
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<tr>
<td>Further adjusted ***</td>
<td>1.3 (0.62–2.6)</td>
<td>0.50</td>
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</tbody>
</table>

* Age adjusted as a continuous variable. ** Adjusted for age (continuous), education (8th grade graduate/some high school/high school grad/some college), sex, race (White/Black/Mexican American/Other), and smoking (current/former/never). *** All the above plus BMI (continuous), glucocorticoid use (yes/no), physical inactivity (yes/no), below poverty indicator (yes/no). † Alternative classification 1: revised ACR criteria for RA. †† Alternative classification 2: allows several substitutions for missing values in the ACR criteria for RA substituting metacarpophalangeal and wrist swelling for missing radiographs and RF, respectively.
multivariable models, and in our sensitivity analyses, we excluded participants currently using glucocorticoids. However, because data were only available for recent steroid use, short- and long-term past use could not be evaluated.

The RA classification method used in this study may introduce misclassification, as subjects with inactive disease or in remission may be missed, and radiographic data were unavailable to evaluate residual joint deformity. However, extensive training of medical staff and interviewers, as well as multiple validation processes by the NHANES staff, suggests that any such misclassification would be nondifferential. To address this limitation, the primary classification of RA used a more flexible definition that included self-reported disease and prescription use; however, this did not include past short- or long-term medication use. Therefore the prevalence of RA may be an underestimate of the true burden of disease in the population. It is possible that participants with severe disease were missed because they were unable to go to the medical center for examination, potentially causing further underestimation of the prevalence of disease in the population. The relatively low levels of inflammation as represented by CRP and the low prevalence of RF among participants with RA may support this. It is also possible that other inflammatory arthritides treated with DMARD may be misclassified as RA. While this misclassification is possible, it is unlikely to contribute a great number of false RA cases since only 12 additional cases were identified by these less strict criteria. Lastly, there may also be nondifferential misclassification of the diabetes, biasing the findings toward the null.

Although more than 35,000 subjects were included in NHANES III, our analysis, restricted to participants aged ≥ 60 years who underwent upper extremity joint examination, identified only 144 participants with RA and 24 who also had DM, severely limiting the statistical power of the study. Sensitivity analyses using the 5 multiple imputation datasets made available by NHANES yielded similar findings, despite the slight increase in subjects included in the analyses.

Given the sample size and the small number of participants with prevalent RA and diabetes, and the resulting wide confidence intervals, we can conclude that this study rules out a strong association, but cannot definitively exclude a modest non-null association. Future longitudinal studies with larger numbers of participants with RA and diabetes are needed to examine temporality and consider the possibility of a modest association.

REFERENCES
1. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-34.