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The association of parity with osteoarthritis and knee replacement in the Multicenter Osteoarthritis Study

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SUMMARY

Objective: We evaluated the association of parity to both risk of knee replacement (KR) and knee osteoarthritis (OA).
Design: The NIH-funded Multicenter Osteoarthritis Study (MOST) is a longitudinal observational study of persons age 50–79 years with either symptomatic knee OA or at elevated risk of disease. Baseline and 30-month knee radiographic OA (ROA) was defined as Kellgren/Lawrence (K/L) grade ≥2 or KR. Women were grouped based by number of births: 0; 1 (reference group); 2; 3; 4; and 5 or more. We examined the relation of parity to the incidence over 30 months of ROA and KR using a Poisson regression model. Generalized estimating equations (GEE) were used to control for correlation between two knees within a subject. We adjusted for age, BMI, race, education, occupation, baseline estrogen use, clinical site, injury, and for KR analyses WOMAC pain and use of pain medication.
Results: Among 1618 women who reported parity information, mean age was 62.6 years, mean BMI 30.7 kg/m^2, mean WOMAC pain subscale score 3.7 at baseline. There were 115 KRs and 134 cases of incident knee ROA over 30 months. The relative risk of incident KR was 2.7 times as high (95% CI: 1.0, 7.3) and relative risk of incident knee ROA was 2.6 times as high (95% CI: 1.2, 5.3) among women with five to 12 children compared with those with one birth.
Conclusion: Parity in women at risk for OA is associated with both incident ROA and KR, particularly for those with more than four children.

Introduction

Osteoarthritis (OA) is the most common cause of disability in the elderly, and has a higher prevalence in women as compared with men. The reasons for this remain unclear, although differences in hormonal milieu have been suspected[1,2].

The most definitive treatment for knee pain is knee replacement (KR). In general, the decision to replace a knee rests on the severity of pain and limitations of function, and often surgeons and patients together make a joint decision on replacement. In a postal survey of orthopedists, most reported severe daily pain with radiographic joint space narrowing as the most common reason they performed KRs[3]. Race, age and gender have all been identified as affecting the likelihood of a particular patient receiving a joint replacement[4], and thus likely confounding the relation between pain and KR. Despite these prior findings, the complex interaction of physical disease characteristics, medical practice approaches, and cultural and individual choices that combine to lead to KR continues to require exploration.

Recently, a large prospective study of 1.3 million women from England revealed that both parity and hormone replacement therapy were associated with joint replacement. Specifically, each additional birth increased the relative risk of KR by 8%[5]. However,

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the investigator did not examine the association of parity with radiographic OA (ROA), a major risk factor for KR.

In order to confirm an increased risk for KR with parity in the USA, we evaluated the relation of number of births to incidence of KR among women participants in the Multicenter Osteoarthritis Study (MOST). In addition, we assessed whether parity was associated with an increased incidence of ROA over 30 months.

Methods

The MOST is an NIH-funded study of risk factors for individuals with or at risk of knee OA due to factors including obesity, knee pain, aching or stiffness on most of the previous 30 days, a history of knee injury or a history of knee surgery. 3026 subjects, age 50–79 years at enrollment were recruited from the areas surrounding Birmingham, Alabama and Iowa City, Iowa. A detailed description of the study population has been published previously[6].

Knee OA was assessed at baseline and at 30 months using weight-bearing fixed flexion in positioning frame posteroanterior X-rays. Two experienced readers blinded to parity status interpreted these paired baseline and 30-months radiographs as part of a central reading process, with excellent reliability (weighted kappa for inter-rater reliability for Kellgren/Lawrence (K/L) grade equal to 0.90)[7,8]. Disagreements were adjudicated by discussion and consensus between the two readers. In this study we defined tibiofemoral knee OA as K/L grade greater than or equal to 2.

KR was assessed by self-report at baseline and at 30-month visits. The self-report was confirmed by radiograph or by medical record documentation. Parity was assessed by self-report at the 30-month clinic visit with the question "how many children did you give birth to?"

Covariates used in this analysis were collected by questionnaire at baseline in the MOST study and were chosen because they might affect either ROA or risk of KR, along with estrogen use which the prior study by Liu *et al.* had examined. These covariates included age, body mass index (BMI), race, educational attainment, occupation (skilled, unskilled/semi-skilled labor, sales, farming, technician, and worked in the home were classified as "labor"; office/clerical and office/professional were classified as "not labor"; all other occupations were classified as "other"), baseline Western Ontario McMaster (WOMAC) pain subscale scores, clinic site, use of estrogen for hormone replacement therapy at baseline (based on information collected in the medication inventory form: the participants "brought in or identified ALL prescription and over-the-counter medications that they took during the last 30 days". Subjects with any use of estrogen during the prior 30 days were considered as users), pain medication use (again based on information collected in the medication inventory form: subjects with any use of analgesics, narcotic analgesics, COX II inhibitors, or NSAIDS during the prior 30 days were considered as users), and history of knee injury or surgery to the knee. BMI was collected during the first clinical assessment.

We examined the relation of number of births to prevalence of ROA and KR at baseline, as well as to incidence of ROA and KR over a 30-month follow-up period. For the cross-sectional study, we included the knees of all women with baseline radiographs who also answered the questions about pregnancy. For the incidence study, we included the knees of all women who had readable radiographs at both baseline and 30 months.

The potential knees included in the joint replacement analysis are those which had no KR at the baseline examination and for which we have information at 30 months on whether a KR was performed in the interval. We defined baseline ROA as including baseline KR, and incident ROA as including incident KR. We defined incident ROA as K/L $\geq$2 at follow-up among knees that had K/L = 0 or 1 at baseline.

Statistical analysis

We divided parity into six categories: zero children; one child (report of one child served as the referent group in all analyses); two children; three children; four children; and five or more children. Using an analysis of variance for continuous variables and a chi-square test for categorical variables, we compared the characteristics of the participants according to parity categories. We examined the relation of parity to prevalence of baseline ROA and to incident ROA over 30 months and incident KR over 30 months with a log linear regression model using the Poisson assumption and robust variance estimates for KR and ROA, respectively. Generalized estimating equations (GEE) were used to account for the correlation between two knees within a person. In the regression model, we adjusted for age, BMI, race, educational level (in three levels: high school graduate or below, some college, college graduate or above), occupation (manual labor vs non-labor vs "other"), baseline WOMAC pain subscale scores, clinic site, estrogen use, history of knee injury or surgery. Age and BMI and WOMAC were entered into the regression model as continuous variables.

This analysis was in compliance with the Helsinki Declaration. The MOST Study was performed at clinical centers at University of Alabama, Birmingham, and University of Iowa with the Coordinating Center at University of California, San Francisco, the Analysis Center at Boston University, and with the first and last authors at University of California, Davis; the appropriate institutional review boards granted approval for the analysis and for the MOST study. All analyses were done using SAS version V9.2 (SAS Institute Inc., Cary, NC, USA) and analyses performed at the 5% significance level.

Results

Of 1820 women enrolled at baseline, 202 were excluded from this analysis because of missing information on parity ($n = 200$, mostly because they were lost to follow-up so could not provide parity information at the second visit) or had rheumatoid arthritis ($N = 2$). Total loss to follow-up from baseline to 30 months in MOST was 198 participants, and all of these subjects were excluded from this analysis. The total number of subjects included in this analysis was 1618 women. The women included in this analysis had a mean age of 62.6 (SD 7.9), mean BMI of 30.7 (SD 6.3) and 83.6% were Caucasian. Participants overall had a mean of 2.5 children (SD = 1.7). As shown in Table I, women with five to 12 children had lower education levels, were more likely to be African American, and were more likely to be in labor occupations than women with fewer children. No significant differences were noted between parity categories for BMI or WOMAC pain levels (See Tables I and II). At baseline there were 45 prevalent KRs; over the 30 months there were 115 incident KRs reported, 113 of which were confirmed by radiograph or by medical documentation. 1244 knees had prevalent ROA at baseline. 129 knees developed incident ROA during 30-month follow-up.

When we dichotomized simple baseline K/L grade by $\geq$2 vs <2 and performed the Chi-square test, the *P*-value was significant for difference by parity ($P < 0.0001$). We found a small but statistically significant increased prevalence of baseline ROA in all women with three or more births compared with those who had one birth (Table III). We also found a statistically significant increased relative risk of incident ROA over 30 months in women with five to 12 births as compared with women with one birth, but no association for other levels of parity (Table IV). Very similar relative risk levels and significance levels were observed when baseline or incident ROA were evaluated without including KR (results not shown).

We also found that women with three or five to 12 children were significantly more likely to have incident KR at 30 months, and it

Table I
Baseline characteristics among 1618 women by parity groups

	All ($N = 1618$)	# of children						*P*-value for comparison among # of children groups
		0 ($N = 210$)	1 ($N = 181$)	2 ($N = 514$)	3 ($N = 372$)	4 ($N = 191$)	5-12 ($N = 150$)	
Age, mean (SD)	62.6 (7.9)	61.1 (8.2)	60.9 (7.9)	60.9 (7.4)	63.4 (7.7)	65.0 (7.1)	67.5 (6.8)	<.0001
BMI, mean (SD)	30.7 (6.3)	31.2 (6.5)	30.9 (6.8)	30.3 (6.2)	30.7 (6.6)	31.0 (5.7)	31.2 (6.0)	0.3798
Race, *N* (%)								
African American	245 (15.1)	22 (10.5)	42 (23.2)	83 (16.1)	44 (11.8)	31 (16.2)	23 (15.3)	0.0038
White	1352 (83.6)	186 (88.6)	133 (73.5)	426 (82.9)	325 (87.4)	156 (81.7)	126 (84.0)	
Other	21 (1.3)	2 (0.9)	6 (3.3)	5 (1.0)	3 (0.8)	4 (2.1)	1 (0.7)	
Educational level, *N* (%)								
High School or less	475 (29.3)	23 (22.7)	41 (22.7)	139 (27.0)	128 (34.4)	80 (41.9)	64 (42.7)	
Some College	472 (29.2)	69 (38.1)	69 (38.1)	154 (30.0)	115 (30.9)	42 (22.0)	46 (30.7)	<.0001
College Graduate or Higher	671 (41.5)	71 (39.2)	71 (39.2)	221 (43.0)	129 (34.7)	69 (36.1)	40 (26.7)	
Occupation, *N* (%)								
Not labor	774 (47.8)	134 (63.8)	100 (55.3)	265 (51.6)	149 (40.1)	81 (42.4)	45 (30.0)	
Labor	465 (28.7)	29 (13.8)	40 (22.1)	120 (23.3)	142 (38.2)	68 (35.6)	66 (44.0)	<.0001
Other	379 (23.4)	47 (22.4)	41 (22.7)	129 (25.1)	81 (21.8)	42 (22)	39 (26.0)	
Pain medication use, *N* (%)	1126 (69.6)	132 (62.9)	128 (70.7)	355 (69.1)	265 (71.2)	140 (73.3)	106 (70.7)	0.2628

appeared that there was a linear trend in the data, where those with more children were more likely to have KR (see Table V). There was no apparent association between estrogen use and risk of KR (RR = 1.3 (0.8, 2.1); $P = 0.3151$).

Discussion

We confirmed an association between parity and incident KR, and found an association between parity and incident and prevalent ROA. The association between parity and risk of KR may be attributable to OA status, changes in weight and body composition, social, neurological, hormonal or other factors.

Liu *et al.* found an 8% per birth increased relative risk for incident KR over a mean of 6.1 years. Liu utilized the Million Women Study, a prospective study of 1.3 million middle-aged women recruited in 1996–2001 through the United Kingdom National Health Service. Liu assigned the nulliparous group as the reference group and then divided the cohort into levels of parity of 1, 2, 3, and "4 or more" births, finding an increased risk in each of those groups compared with nulliparous women. They also examined a variety of other factors related to hormonal milieu, including oral contraceptive use, hormone replacement therapy, age at menarche and age at menopause, and found a significant association only with current hormone therapy use and age at menarche. However, due to limited covariate information, they were not able to address whether parity is associated with increased risk of OA itself, the primary diagnosis engendering KR, and they were not able to adjust for potentially important covariates, such as occupation and history of injury to the joint[5]. In the MOST, a longitudinal study of risk factors for knee OA, we collected additional data including careful radiologic evaluation of all knees, history of joint injuries, and occupation.

The specifics of the MOST population indicate that the associations we have identified between parity and OA may or may not hold true in a more general population. It is of some interest that Liu *et al.* identified an association with KR in a general population, but it may be that the associations in the two different populations reflect different mechanisms by which pregnancy increases relative risk.

Jorgensen *et al.* recently reported that an increasing numbers of live births reported by both men and women was associated with increased risk of "first OA hospitalization" in a Danish cohort using International Classification of Diseases (ICD) codes for their definition of OA[9]. Physician clinical diagnosis assessed by ICD codes carries the potential for misclassification bias. The direct diagnosis of radiographic knee OA and KR in the current study avoids this type of bias. In addition, the effect was observed in both men and women in the Danish cohort, which may suggest that childrearing factors (carrying children, etc.) are an important contributor to the increased OA risk; unfortunately we do not have information in MOST on number of children for men.

Wei *et al.* performed a cross-sectional study of 489 women and found that increased number of live or still births was associated with decreased total knee cartilage volume on MRI but not with

Table II
Baseline knee-based radiographic characteristics, history of knee injury or surgery and WOMAC knee pain

	All ($N = 1618$)	# of children						*P*-value for comparison among # of children groups
		0 ($N = 210$)	1 ($N = 181$)	2 ($N = 514$)	3 ($N = 372$)	4 ($N = 191$)	5–12 ($N = 150$)	
K/L grade*, (%)								
0	43.5	44.3	49.4	46.6	41.4	41.5	32.9	
1	17.4	19.4	18.4	19.3	14.4	15.6	16.1	0.4456
2	15.5	16.0	12.6	13.8	18.5	17	15.1	
3–4	23.6	20.3	19.6	20.2	25.8	25.9	35.9	
Knees with history of injury or surgery, (%)	25.7	28.6	27.4	23.9	26.5	25.4	23.7	0.5095
WOMAC knee pain subscale (0–20)	3.7 (3.8)	3.4 (3.6)	3.7 (4.0)	3.4 (3.7)	4.0 (3.9)	3.8 (4.0)	3.7 (3.9)	0.0731

*For the K/L grade listings, 53 knees had K/L grade missing, 45 had KR at baseline, eight excluded from knee X-ray reading due to osteonecrosis or poor film quality.

Table III
Parity and baseline prevalent radiographic knee OA, including KR

Number of births	Total # knees	# (%) with ROA	Crude	Age, BMI, race-adj.		Multi-adj.*	
			RR	RR	*P*-value	RR	*P*-value
0	416	153 (36.78)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	0.2133	1.2 (0.9, 1.5)	0.1952
1 (ref)	362	119 (32.87)	1.0	1.0		1.0	
2	1028	360 (35.02)	1.1 (0.9, 1.3)	1.2 (0.9, 1.4)	0.1527	1.2 (1.0, 1.4)	0.1177
3	742	335 (45.15)	1.4 (1.1, 1.7)	1.3 (1.1, 1.6)	0.0052	1.3 (1.1, 1.6)	0.0063
4	380	168 (44.21)	1.3 (1.1, 1.7)	1.2 (1.0, 1.5)	0.0725	1.2 (1.0, 1.5)	0.0770
5–12	300	154 (51.33)	1.6 (1.2, 2.0)	1.3 (1.0, 1.6)	0.0405	1.3 (1.0, 1.6)	0.0420

* Adjusted for age, BMI, race, education, occupation, injury/surgery, estrogen use, clinical site. KR was considered to be prevalent ROA.

joint space narrowing or osteophytosis on radiograph in adjusted analyses[10]. They also found "no association between parity and change in either cartilage volume or cartilage defects over 2.7 years". The authors stated "this might be expected given that pregnancy was an exposure in the relatively distant past". Although our measures of OA, using radiographs, are obviously different from cartilage volume measurements on MRI, it is interesting that they found no association with cartilage change over time, where we found significant evidence of incident OA disease over a similar timespan. It is possible that this is due to smaller numbers of subjects in Wei's study, or due to a different population in Tasmania, Australia which may have different genetic risks and different cultural approaches to occupation or childrearing. It is also worth noting that the MOST women were recruited specifically because they either had knee OA or were at high risk of the disease, where the Tasmanian subjects were recruited from a general health study cohort.

A relationship between parity and KR might be due to increased risk of OA. The fact that we found a significant association with incident and prevalent ROA supports the idea that at least part of the increased risk of KR may be related to the observed increase in radiographic disease. The similarity of effect size magnitudes in the associations between parity and ROA and between parity and KR suggest that ROA is an important and perhaps dominant factor, perhaps more important than social factors related to community and family size, exposure to community members who have had joint replacements, differences in willingness to consider surgery, and other such factors. It is unclear why the association for the group with four children did not reach significance while the three and five to 12 children groups were significant, but it may be due to variations inherent in the relatively small outcome numbers in this analysis.

The relationship between parity and incident ROA is interesting, and suggests that there may be biological events during pregnancy or childrearing which do not manifest as incident disease until many decades after the pregnancies. These may include damage to cartilage due to extra weight carried or increased "clumsiness" during pregnancy due to the temporary alteration of weight distribution, which may predispose to later disease without overtly causing it at the time of pregnancy. Alternatively, rather than direct damage to joints that occurs during pregnancy, it is possible that permanent changes occur in the body during pregnancy which predispose to adverse joint health in the decades following reproductive life. These changes may include additive weight retention after pregnancy[11] or hormonal changes or other factors, perhaps acting in a "multi-hit" model. Although we adjusted for BMI in the current study, it was not possible to adjust for BMI prior to entering the MOST study. It is also worth noting that despite some controversy, there is evidence that excess weight gain may occur after first pregnancy but not after further pregnancies[12–16]; our finding of increasing risk of ROA with increasing numbers of births suggests that weight gain after pregnancy is not sufficient to explain the patterns of ROA we see. It is also possible that caring for children causes ongoing physical insults to the joints during childrearing years, which again may only manifest years later. In this sense, pregnancies might be considered to be a period of "injury" (due to transient increased weight, hormonal changes, etc) similar, for example, to ligamental or meniscal injuries which predispose to the disease of OA later in life. Other potential sources of residual confounding, such as differential occupational exposures by parity group, are also possible.

A number of earlier studies found no association between knee OA and parity or pregnancy[17–19]. However, these studies differed in significant ways from ours. Dawson *et al.* examined the number of full term pregnancies, but had relatively small numbers of subjects and assigned parity levels differently, dividing into 0–2, 3, and >3[18]. Samanta *et al.* did not have knee OA as a specific outcome but instead used "large joint OA" as an outcome and "ever-pregnant" or "live birth" as the risk factor, finding no association[19]. Anderson and Felson found a non-significant 5% per birth increased risk of ROA of the knee in the NHANES I dataset in an age-adjusted analysis, possibly due to the fact that non-weight-bearing AP knee films were used in that study[17]. It is not entirely clear why each of these earlier studies failed to find an association where our study did, but it is likely because of differences in variable definition or collection, or in the populations studied.

It is important to consider that the question asked of the women in MOST was "how many children did you give birth to" rather than, for example, "how many times were you pregnant?" In Liu's study, she found an increased risk of joint replacement with hormone

Table IV
Parity and incident ROA over 30 months, including new KR

Number of births	Total # knees	# (%) with ROA	Crude	Age, BMI, race-adj.		Multi-adj.*	
			RR	RR	*P*-value	RR	*P*-value
0	263	18 (6.84)	1.3 (0.6, 2.7)	1.2 (0.6, 2.6)	0.5628	1.3 (0.6, 2.7)	0.5358
1 (ref)	241	13 (5.39)	1.0	1.0		1.0	
2	657	40 (6.09)	1.1 (0.6, 2.2)	1.2 (0.6, 2.4)	0.5128	1.3 (0.7, 2.5)	0.4087
3	407	29 (7.13)	1.3 (0.7, 2.6)	1.4 (0.7, 2.7)	0.3523	1.5 (0.8, 3.0)	0.2291
4	212	17 (8.02)	1.5 (0.7, 3.2)	1.5 (0.7, 3.1)	0.2945	1.7 (0.8, 3.6)	0.1459
5–12	143	17 (11.89)	2.2 (1.1, 4.6)	2.1 (1.0, 4.5)	0.0489	2.6 (1.2, 5.3)	0.0120
P for linear trend							0.0258

* Adjusted for age, BMI, race, education, occupation, injury/surgery, estrogen use, clinical site. New KR was considered to be incident ROA.

Table V
Parity and 30-month incident KR

Number of births	Total # knees	# (%) with incident KR	Crude	Age, BMI, race-adj.		Multi-adj.*	
			RR	RR	*P*-value	RR	*P*-value
0	417	6 (1.44)	0.7 (0.2, 2.2)	0.7 (0.2, 2.3)	0.5540	0.9 (0.3, 2.9)	0.8580
1 (ref)	358	7 (1.96)	1.0	1.0		1.0	
2	1013	33 (3.26)	1.6 (0.7, 4.0)	1.8 (0.7, 4.5)	0.2398	2.0 (0.8, 5.1)	0.1624
3	732	38 (5.19)	2.6 (1.1, 6.4)	2.4 (1.0, 6.1)	0.0594	2.7 (1.1, 6.8)	0.0375
4	373	14 (3.75)	1.9 (0.7, 5.2)	1.7 (0.6, 4.8)	0.3199	1.8 (0.6, 5.3)	0.2590
5–12	298	17 (5.70)	2.8 (1.1, 7.5)	2.2 (0.8, 6.2)	0.1299	2.7 (1.0, 7.3)	0.0494
P for linear trend							0.0070

* Adjusted for age, BMI, race, education, occupation, WOMAC knee pain, pain medication, estrogen use, clinical site.

replacement therapy, a finding which we did not see in our dataset; this could be due to differences in the subject populations in terms of age or other factors, differences between "hormone replacement therapy" (as defined in Liu) and "estrogen use" (as defined in MOST), or simply a smaller sample size in the MOST Study. However, there is no information about age at menarche and menopause, breastfeeding history, number of pregnancies, and other hormonal factors in the MOST dataset, and exploring these factors might potentially elucidate our findings.

Some readers may be interested in how our results would have differed if we had used nulliparous women as the referent group. We have redone the analysis using no children as referent point and we provide the results as Online Appendix Tables A1–A3 for your inspection. The same general patterns hold in this alternate analysis, but because women with zero children systematically have slightly higher risk of ROA and of KR than do women with one child, some of the results become statistically insignificant. Given known and likely unknown differences between women with zero births and all other women, we have presented the analysis using women with one birth as referent as our core results and we believe this serves to highlight the patterns of relative risk.

Given that some women were missing information on parity, we considered whether missing information on parity may potentially bias the association of parity and incident ROA. Since women who did not come to the 30 month visit had no information on parity, we took an indirect approach by using all women who do have parity data available at the 30-month visit and testing if parity is associated with loss to follow-up at the 60-month visit. After adjusting for age, BMI, race and clinic site, compared with nulliparous women, the relative risk of loss to follow-up for those with one, two, three, four, and five to 12 children were 1.1, 1.1, 1.2, 1.0, and 1.2, respectively (all *P*-values >0.50) (see Table A4 in the Online Appendix). These findings indicate that parity is not significantly associated with risk of loss to follow-up. Thus, we believe that missing information may have only a limited impact on the effect estimates, although these findings provide only indirect evidence on this potential bias.

Perhaps the most important limitation of our study is that the MOST cohort may not be representative of the general population of women who experience pregnancy due to the inclusion criteria employed for the study, and therefore our findings may not be as generalizable as some larger cohorts. Although it is one of the largest comprehensive prospective cohorts organized around questions of OA, there are still only a limited number of the outcomes, which may have prevented reaching significance for some of the questions. Some parity groups had small numbers of outcomes. 30 months is a relatively short time for observing for incident OA outcomes.

There are also important strengths in our study, which include a large longitudinal dataset of over 1800 women in which risk factors, radiographs and information on joint replacement has been obtained in a standardized, comprehensive manner. The radiographs have been read by central readers in this cohort and have excellent reliability. Loss to follow-up has been extremely low in this cohort, so the incident results are robust and subject to relatively little of this type of bias.

In summary, increasing numbers of births in women with or at high risk for knee OA is associated with increased risk of prevalent ROA and incident KR and ROA. The observation of new cases of ROA late in life associated with pregnancy earlier in life suggests that the effect of pregnancy or children continues to express itself decades after the pregnancy and may reflect a model of joint injury engendering OA in later years.

Author contributions

Concept and design: BLW, JN, YZ, NEL.
Acquisition of data: MN, DTF.
Analysis and interpretation of data: BLW, JN, YZ, LB, NS, JK, MN, NEL.
Preparation and revision of manuscript: BLW, JN, YZ, LB, NS, JK, MN, NEL.
Final approval of submitted version: BLW, JN, YZ, DTF, LB, NS, JK, MN, NEL.

Conflict of interest

Drs Wise and Zhang have received research funding from Pfizer, Inc. for work unrelated to the present manuscript.

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Supplementary data

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