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ORIGINAL ARTICLE

Association of Low Birth Weight and Preterm Birth With the Incidence of Knee and Hip Arthroplasty for Osteoarthritis

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Objective. **Low birth weight (LBW) and preterm birth have been associated with adverse adult outcomes, including hypertension, insulin resistance, cardiovascular disease, and reduced bone mass. It is unknown whether LBW and preterm birth affect the risk of osteoarthritis (OA). This study aims to examine whether LBW and preterm birth were associated with the incidence of knee and hip arthroplasty for OA.**

Methods. **A total of 3,604 participants of the Australian Diabetes, Obesity and Lifestyle Study who reported their birth weight and history of preterm birth and were age >40 years at the commencement of arthroplasty data collection comprised the study sample. The incidence of knee and hip replacement for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry.**

Results. **One hundred and sixteen participants underwent knee arthroplasty and 75 underwent hip arthroplasty for OA. LBW (yes versus no; hazard ratio [HR] 2.04, 95% confidence interval [95% CI] 1.11–3.75, $P = 0.02$) and preterm birth (yes versus no; HR 2.50, 95% CI 1.29–4.87, $P = 0.007$) were associated with increased incidence of hip arthroplasty independent of age, sex, body mass index, education level, hypertension, diabetes mellitus, smoking, and physical activity. No significant association was observed for knee arthroplasty.**

Conclusion. **Although these findings will need to be confirmed, they suggest that individuals born with LBW or at preterm are at increased risk of hip arthroplasty for OA in adult life. The underlying mechanisms warrant further investigation.**

INTRODUCTION

Osteoarthritis (OA) is a major public health problem and the most common cause of disability, with OA of the knees and hips resulting in a total of 71.1 million years lived with disability in 2010, an increase of 64% since 1990 globally (1). Currently there are no registered disease-modifying OA drugs. Therefore, understanding the risk factors for OA is important for improving prevention.

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Significance & Innovations

- Low birth weight (LBW) and preterm birth have been associated with adverse outcomes in adulthood, including hypertension, insulin resistance, and cardiovascular disease, and more recently reduced bone mass.
- It is unknown whether LBW and preterm birth affect the risk of osteoarthritis (OA).
- This study finds out that LBW and preterm birth are risk factors for hip OA, but not knee OA, requiring arthroplasty.
- Individuals with LBW or preterm birth should be identified as an "at risk group" and targeted for close monitoring of hip OA.

Low birth weight (LBW) and preterm birth have been associated with adverse outcomes in adulthood, including hypertension, insulin resistance, cardiovascular disease (2), and more recently reduced bone mass (3). As an underlying mechanism, fetal nutrition in utero leading to reprogramming of the insulin-like growth factor 1 (IGF-1) axis has been proposed (4,5). IGF-1 stimulates osteoblastic differentiation of mesenchymal stem cells and new bone formation, and therefore maintains proper bone microarchitecture and mass (6).

Whether LBW and preterm birth affect the risk of OA is unknown. However, acetabular dysplasia has been linked with preterm birth (7,8), and mild acetabular dysplasia is associated with an increased incidence of hip OA (9–11). There is increasing evidence suggesting that hip and knee OA are susceptible to different risk factors (12). Given the bony changes associated with LBW and preterm birth, we hypothesized that they would be associated with hip rather than knee OA.

Studies exploring knee or hip OA have generally defined OA using imaging modalities (9–11). Another method for defining OA is based on arthroplasty (12), which has been shown to be useful for identifying the potential risk factors for knee and hip OA (12). This definition signifies severe knee and hip OA, which is relevant to the symptomatic disease burden and health economics. Therefore, the aim of this study was to determine whether LBW and preterm birth were associated with the incidence of knee and hip arthroplasty as measures of severe OA in a prospective cohort study.

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MATERIALS AND METHODS

Study participants. The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study is a national, population-based cohort study of 11,247 people, age ≥25 years, recruited by a stratified cluster-sampling method involving 7 strata (6 states and the Northern Territory) and clusters based on census collector districts during 1999–2000. In 2004–2005, a 5-year followup survey was conducted. All eligible participants included in the baseline survey were invited (n = 10,788), of whom 7,157 (66.3%) responded (Figure 1). Detailed methods and response rates were described previously (13). The study was approved by the International Diabetes Institute Ethics Committee (13).

For the current study, participants were restricted to those age ≥40 years at the commencement of data collection by the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR), January 1, 2002 since arthroplasty as the treatment of OA is very uncommon under this age (14). Of the 7,157 participants, 950 were excluded as they were age <40 years or had the first recorded arthroplasty as a revision surgery, leaving 6,207 participants eligible for the current study (Figure 1). The data linkage study was approved by the Alfred Hospital Ethics Committee and the University of Adelaide and Monash University Human Research Ethics Committees.

Demographic and lifestyle factors, and anthropometric and clinical measurement. Demographic and lifestyle data, including date of birth, sex, smoking, and physical activity, were collected in 1999–2000 by trained interviewers using standardized questionnaires (13). Height was measured to the nearest 0.5 cm without shoes using a stadiometer. Weight was measured without shoes and in light clothing to the nearest 0.1 kg using a mechanical beam balance. Body mass index (BMI) was calculated in kilograms per square meter (13). Blood pressure was measured with a Dinamap/mercury sphygmomanometer (13). Hypertension was defined as blood pressure >140/90 mm Hg or current use of antihypertensive medication (13).

Blood was drawn after an overnight fast (≥9 hours) for measurement of glucose followed by a 2-hour, 75-gram oral glucose tolerance test. All specimens were analyzed at a central laboratory. Fasting plasma glucose (FPG) and 2-hour postload glucose were analyzed by an automated glucose oxidase method (Olympus Optical). Diabetes mellitus was defined if participants were on antidiabetic medication, or if they had an FPG ≥7.0 mmol/liter, or a 2-hour postload glucose ≥11.1 mmol/liter (15).

LBW and prematurity. At the 2004–2005 followup, participants were asked to state their birth weight and whether they were born ≥2 weeks preterm (2). Participants were also asked to indicate the likely accuracy and source of their answers (2). Of the 6,207 eligible participants, 3,604 reported a value for birth weight and preterm birth, with the others unable to give a value. More than 90% of respondents who reported a birth weight considered it to be "accurate" and only 6% were based on a

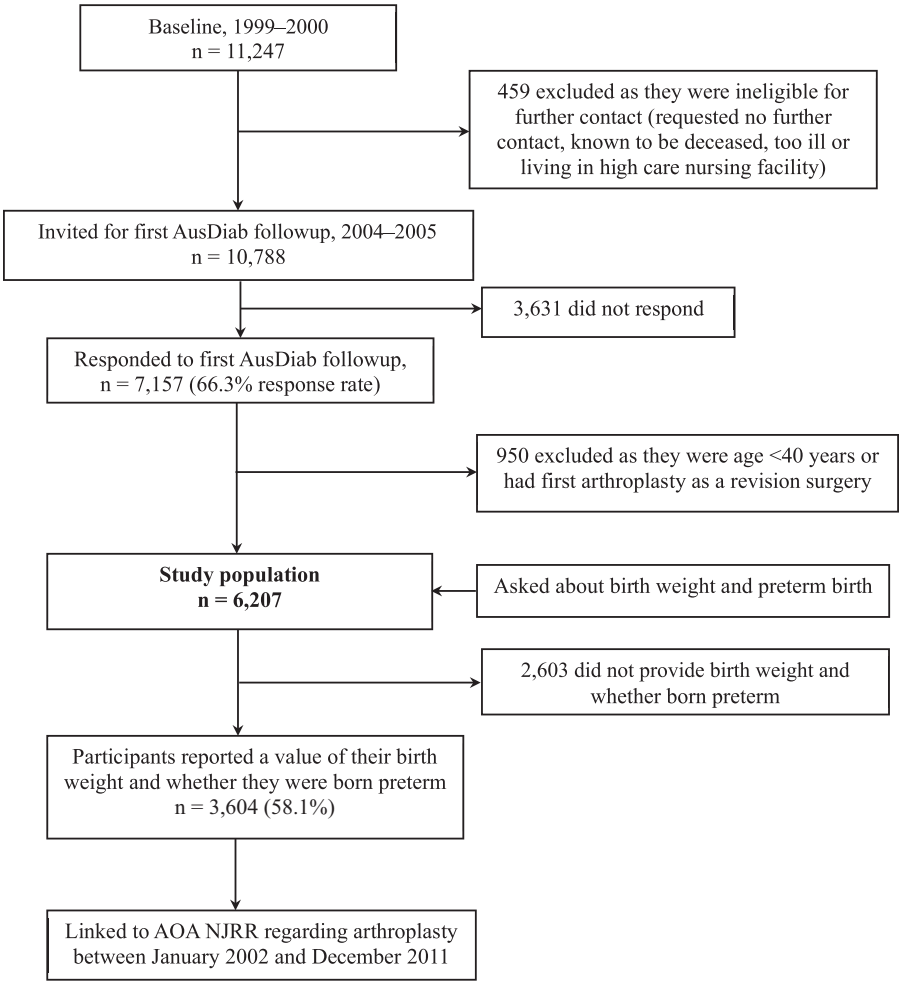

Figure 1. Flowchart of recruited participants from The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. AOA NJRR = Australian Orthopaedic Association National Joint Replacement Registry.

"guess"; 80% obtained their birth weight from a family member (67% of participants had a living natural mother and 46% a living natural father) and 10% from medical records (2). Detailed information on accuracy and validity of self-reported LBW and preterm birth was previously described (2). LBW was defined as birth weight <2.5 kg.

Participants who reported their birth weight were younger (mean ± SD 49.6 ± 12.6 versus 53.3 ± 15.8 years; $P < 0.001$), less likely to have diabetes mellitus (6.4% versus 10.6%; $P < 0.001$) and hypertension (28.2% versus 37.0%; $P < 0.001$), and had lower BMI (mean ± SD 26.9 ± 4.9 versus 27.1 ± 5.1 kg/m^2; $P = 0.05$) compared with individuals who did not respond to the questionnaire or could not recall their birth weight. However, when the risk of arthroplasty of those who reported their birth weight versus those who did not was compared, there was no difference in risk of knee (2.8% versus 2.8%) or hip (1.9% versus 1.8%) arthroplasties for OA ($P > 0.80$ for all).

Identification of incident primary knee and hip arthroplasty. Cases were identified from the AOA NJRR as those who underwent either a primary hip or a primary knee arthroplasty. Detailed information is available in the AOA NJRR on prostheses, patient demographics, and type and reason for arthroplasty (such as OA, rheumatoid arthritis, fracture, etc.). Data are collected from both public and private hospitals and validated using a sequential multilevel matching process against State and Territory Health Department unit record data (16). Following the validation process and retrieval of unreported records, the AOA NJRR collects an almost complete set of data relating to hip and knee arthroplasty in Australia (16).

Matching of AusDiab participants using first name, surname, date of birth, and sex, to the AOA NJRR in order to identify those who had had a primary arthroplasty performed between January 1, 2002 and December 31, 2011 was performed using US Bureau of the Census Record Linkage Software.

Definition of knee and hip OA. Knee or hip OA was defined as the first primary knee or hip arthroplasty with a contemporaneous diagnosis of OA, as recorded in the AOA NJRR (17). If one person had multiple arthroplasties, such as bilateral knee arthroplasty, bilateral hip arthroplasty, or both knee and hip arthroplasties, the first recorded procedure was considered the event.

Table 1. Characteristics of study population*

	No arthroplasty (n = 3,413)	Knee arthroplasty (n = 116)	Hip arthroplasty (n = 75)
Age at baseline, years	51.8 ± 10.0	59.7 ± 9.5	59.0 ± 9.5
Age at 2002, years	54.1 ± 10.0	62.1 ± 9.5	61.3 ± 9.3
Female	2,058 (60.3)	69 (59.5)	45 (60.0)
Body mass index, kg/m^2	26.9 ± 4.9	30.2 ± 5.3	28.7 ± 4.4
Hypertension	981 (28.9)	68 (59.1)	36 (48.0)
Diabetes mellitus	232 (6.7)	14 (12.3)	5 (6.7)
Smoking status			
Nonsmoker	1,929 (57.5)	68 (59.1)	39 (54.2)
Former smoker	1,031 (30.7)	36 (31.3)	25 (34.7)
Current smoker	395 (11.8)	11 (9.6)	8 (11.1)
Physical activity			
Sedentary	484 (14.3)	26 (22.8)	15 (20.3)
Insufficient	1,027 (30.3)	40 (35.1)	19 (25.7)
Sufficient	1,878 (55.4)	48 (42.1)	40 (54.1)
Birth weight (kg)	3.4 ± 0.7	3.5 ± 0.8	3.3 ± 0.7
Low birth weight	303 (8.9)	11 (9.5)	13 (17.3)
Preterm birth	270 (9.5)	8 (8.5)	11 (19.0)

* Values are the number (%) or mean ± SD.

Statistical analysis. Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) for knee or hip arthroplasty due to OA associated with LBW and preterm birth. Followup for arthroplasty (i.e., calculation of person-time) began January 1, 2002 and ended at the date of first arthroplasty for OA or date of censoring. Participants were censored at either the date of first arthroplasty performed for indications other than OA, the date of death, or end of followup (i.e., December 31, 2011, the date that ascertainment of arthroplasty by the AOA NJRR was complete), whichever came first. LBW and preterm birth were analyzed and modelled separately. Each analysis was adjusted for age, sex, and BMI (in model 1), as these are established risk factors for arthroplasty for OA (17). In model 2, the analyses were further adjusted for hypertension, diabetes mellitus, smoking status, and physical activity. To test whether associations of LBW and preterm birth with arthroplasty risk were modified by obesity (BMI ≥30 kg/m^2) and sex, interactions were fitted and tested using the likelihood ratio test. Tests based on Schoenfeld residuals and graphical methods using Kaplan-Meier curves showed no evidence that proportional hazard assumptions were violated for any analysis.

With the sample size of 3,604 participants who had complete data available on birth weight, our study had 80% power (at the 5% significance level, 2-sided significance) to detect a risk ratio of 1.96, where the risk of knee or hip replacement in those without LBW or preterm birth was assumed to be 1.9% and the prevalence of LBW to be 9.0%. All statistical analyses were performed using Stata software, version 12.0.

RESULTS

One hundred and ninety-one arthroplasties (116 knee arthroplasties and 75 hip arthroplasties) performed for OA were identified between January 1, 2002 and December 31, 2011. The mean ± SD followup duration was 9.3 ± 2.1 years. Descriptive characteristics of the study participants are presented in Table 1. Of the 3,604 participants, 122 participants had only LBW, 144 participants were only preterm, and 135 participants had both LBW and preterm birth. The correlation between LBW and preterm birth was 0.45 (Pearson's correlation; $P < 0.001$). Participants who underwent hip arthroplasty were more likely to be born with LBW or preterm than those who did not have hip arthroplasty.

Table 2. Relationship of low birth weight and preterm birth with incidence of knee and hip arthroplasty for osteoarthritis*

	Unadjusted		Adjusted model 1†		Adjusted model 2‡	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Knee arthroplasty						
Low birth weight	1.07 (0.58–1.99)	0.83	0.93 (0.50–1.73)	0.82	0.86 (0.45–1.66)	0.65
Preterm birth	0.88 (0.43–1.81)	0.73	0.97 (0.47–2.00)	0.93	0.79 (0.36–1.73)	0.56
Hip arthroplasty						
Low birth weight	2.14 (1.18–3.90)	0.01	1.87 (1.02–3.41)	0.04	2.02 (1.10–3.73)	0.02
Preterm birth	2.21 (1.15–4.27)	0.02	2.41 (1.25–4.66)	0.009	2.53 (1.30–4.92)	0.006

* HR = hazard ratio; 95% CI = 95% confidence interval.
† Adjusted for age, sex, and body mass index (BMI).
‡ Adjusted for age, sex, BMI, hypertension, diabetes mellitus, smoking, and physical activity.

In age-, sex-, and BMI-adjusted analysis (model 1), both LBW (HR 1.87, 95% confidence interval [95% CI] 1.02–3.41, $P = 0.04$) and preterm birth (HR 2.41, 95% CI 1.25–4.66, $P = 0.009$) were associated with increased incidence of hip arthroplasty for OA. The results remained significant after adding hypertension, diabetes mellitus, smoking, and physical activity to the previous model, for both LBW (HR 2.02, 95% CI 1.10–3.73, $P = 0.02$) and preterm birth (HR 2.53, 95% CI 1.30–4.92, $P = 0.006$) (model 2). In contrast, neither LBW nor preterm birth was significantly associated with the incidence of knee arthroplasty for OA in unadjusted or adjusted analyses (Table 2).

There was no evidence that obesity or sex modified the associations between LBW or preterm birth and arthroplasty risk ($P > 0.10$ for all).

DISCUSSION

This is the first study to report the relationship of LBW and preterm birth with the incidence of severe knee and hip OA requiring arthroplasty in a general population. LBW and preterm birth were associated with increased incidence of hip OA but not knee OA.

No previous studies have examined the association between LBW or preterm birth and the risk of OA. We found an association for hip OA requiring arthroplasty. The etiology of hip OA is multifactorial (18). Both congenital and developmental diseases of the hip, such as mild hip dysplasia, may influence the development of hip OA in adulthood (19,20). The formation of the acetabulum is incomplete at birth in preterm babies (21). Preterm infants often develop a postural deformation of the legs that persists until early childhood (7), perhaps because of an underdeveloped or shallow, upwardly sloping acetabulum (22), decreased joint surface area (9), or because the ligaments holding the ball in place are too loose (7). These factors may influence the development of the hip, resulting in abnormal hip joint shape. The important role of hip bone shape and geometry in the etiology of hip OA has been established (20). Premature and LBW babies represent a unique vulnerable population, in which bone growth and mineral acquisition are critical in regards to bone turnover (23). A case–control study similarly found reduced peak bone mass at the femoral neck in very LBW babies (3). There is emerging evidence that preterm birth and very LBW result in a decrease in bone formation and increase in bone resorption (23,24) that reduced osteoclast apoptosis (25) and cartilage degeneration (26), which may be another potential pathway of development of hip OA.

Although we found a relationship of LBW and preterm birth with hip OA requiring arthroplasty, no relationship was observed for knee OA requiring arthroplasty. These differences support the notion of different susceptibility of these joints to various risk factors (12,27). Therefore, while bone shape and geometry are important in the etiology of hip OA, these factors are less critical than soft tissue and other factors in the pathogenesis of knee OA (20). As LBW and preterm birth have significant impacts on bone and hip structure, this is biologically plausible (7).

Clarifying the mechanisms for the relationship between LBW and preterm birth and hip OA is important. LBW and preterm birth may result in abnormal hip development because these babies are born early and the acetabulum is underdeveloped (21,22). Postdelivery, the hips are extended rather than being maintained in a flexed and abducted in utero position (28,29). This altered hip position may potentially be responsible for an increased incidence or severity of acetabular dysplasia. If this is proven to contribute to the development of hip OA, then modifying hip position through postural support (28,29) and perhaps the use of double diapers (30) may be beneficial for babies born with LBW or preterm, and they may need to be targeted for screening and early treatment of hip dysplasia. As the number of LBW and preterm births is increasing, if they are proven to be at increased risk of hip OA, the impact of proactive strategies to reduce hip OA, such as the prevention of obesity (31), will be greater.

The strengths of our study include its large sample size and prospective design. Although defining OA based on arthroplasty only identifies the tip of the iceberg of the true problem, it signifies the severity of OA, which is relevant to the symptomatic disease burden and health economics (31). Furthermore, the AOA NJRR data are validated and nearly complete regarding arthroplasty in Australia (16). The findings of our study need to be considered within the context of its limitations. Birth weight and preterm birth were self-reported. This might have resulted in recall and rumination bias. However, in this study, there is low scope of recall bias or rumination bias in birth weight or preterm birth in relation to arthroplasty. Birth weight and preterm birth data were collected during the first round of followup of the cohort in 2004–2005. The linkage component of the study in terms of joint replacement for OA was introduced in 2013. When people were asked about their birth status, there was no specific hypothesis that this would be associated with health outcomes, including OA. We didn't ask people if they had LBW. We simply asked them about their weight at birth; many people would not know what a normal birth weight is, so sick people would be unlikely to be able to assign themselves an abnormal result. Previous studies reporting associations of birth weight with adult health have used this technique (2,32–34). Self-reported mean ± SD birth weight in our study was 3.37 ± 0.7 kg, which was similar whether birth weight was obtained from family members or from medical records (mean ± SD 3.35 ± 0.6 versus 3.37 ± 0.7 kg; after adjustment for age and sex; $P = 0.36$) (2). The birth weight of our study population is similar to the recent average Australian birth weight of 3.46 kg for boys and 3.33 kg for girls (35). Individuals with the highest and lowest birth weights tend to report normal birth weight (36), which will lead to underestimation of arthroplasty risk associated with LBW. Nevertheless, we found a significant association of LBW and prematurity with hip but not knee arthroplasty. It is unlikely that any misclassification would affect the relationship with arthroplasty at the hip but not the knee. For example, while participants who reported birth weight and prematurity had better health compared with those who did not respond to the questionnaire or could not recall their birth weight, the risks of both hip and knee arthroplasty were very similar. We did not have arthroplasty data prior to 2002. It is possible that arthroplasties

occurring before 2002 represent more rapidly progressive disease, and inclusion of those data in analysis may influence our findings. Only 1.5% of those who attended the baseline AusDiab study thought that they may have undiagnosed diabetes mellitus. Although this was higher than in those who did not participate, published data show that the absolute number was too small to have any measurable effect even on diabetes mellitus prevalence (37). Again, whether patients undergo arthroplasty as the treatment of OA may be influenced by a number of factors such as access to health care, physician bias, and patient-level factors (38), in addition to disease severity. Australia has a publicly funded universal health system (Medicare) and people without private health insurance have access to joint replacement under this system. We have performed the analysis adjusted for age, sex, BMI, hypertension, diabetes mellitus, smoking, and physical activity to counter this issue. Further adjustment for education and ethnicity did not change the results (data not shown). Moreover, it is possible that there is residual confounding. However, if residual confounding is the main explanation for the association between LBW and preterm birth and OA risk, we would expect the same association for knee and hip arthroplasty, which was not the case as we observed differential effect of LBW and preterm on hip and knee OA.

LBW and preterm birth are associated with an increased risk of hip but not knee OA requiring arthroplasty. This may be via the mechanisms of acetabular dysplasia and reduced bone mass. Although these findings will need to be confirmed in other studies and the underlying mechanisms warrant further investigation, these data suggest that individuals born with LBW or preterm are at increased risk of hip arthroplasty for OA in adult life. Identifying individuals born with LBW or preterm as an "at risk group" for hip OA and targeting them for close monitoring and early interventions may reduce the incidence of hip OA in later life.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Cicuttini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wang, Shaw, Cicuttini.

Acquisition of data. Shaw, Magliano, Graves.

Analysis and interpretation of data. Hussain, Wang, Wluka, Magliano, Cicuttini.

ROLE OF THE STUDY SPONSOR

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