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Postvaccination immune responses and risk of primary total hip arthroplasty—A population-based cohort study

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SUMMARY

Objective: To investigate the relationship between individual postvaccination immune responses and subsequent risk of total hip arthroplasty (THA) due to idiopathic osteoarthritis (OA) or rheumatoid arthritis (RA).

Method: Results of tuberculin skin tests (TSTs) following the Bacille Calmette–Guerin (BCG) vaccination were used as a marker of individual immune responses. TST results from the mandatory mass tuberculosis screening program 1948–1975 (n = 236 770) were linked with information on subsequent THA during 1987–2020 from the Norwegian Arthroplasty Register. The multivariable Cox proportional hazard regression was performed.

Results: A total of 10 698 individuals received a THA during follow-up. In men, there was no association between TST and risk of THA due to OA (Hazard ratio [HR] 1.01, 95% confidence interval [CI] 0.92–1.12 for positive versus negative TST and HR 1.06, 95% CI 0.95–1.18 for strong positive vs negative TST), while the risk estimates increased with increasingly restrictive sensitivity analyses. In women, there was no association with THA due to OA for positive versus negative TST (HR 0.98, 95% CI 0.92–1.05), while a strong positive TST was associated with reduced risk of THA (HR 0.90, 95% CI 0.84–0.97). No significant associations were observed in the sensitivity analysis for women or for THA due to RA.

Conclusion: Our results suggest that an increased postvaccination immune response is associated with a nonsignificant trend of increased risk of THA among men and a decreased risk among women, although risk estimates were small.

Introduction

Osteoarthritis (OA) constitutes a significant global health problem, with around 300 million affected individuals worldwide.[1] High body mass index (BMI) at a young age, higher age, and female gender are all risk factors for developing primary OA.[2,3] In Norway, approximately 20 500 (381 per 100 000) patients undergo joint replacement surgery due to OA yearly, of which 9 800 with a hip arthroplasty.[4]

The vast majority of OA is idiopathic (from here on referred to as OA), with a pathophysiology that is more complex than the previously suspected "wear and tear." One of the involved pathways is thought to include adverse immune responses. Studies show an increased amount of T helper cells and macrophages in the synovial membranes and fluid of affected OA joints in a similar but less pronounced manner to that seen in rheumatoid arthritis (RA).[5,6] Pro-

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inflammatory cytokines and growth factors outweigh the effect of anti-inflammatory cells, resulting in cartilage metaplasia, degradation, and an imbalance between bone formation and resorption.[7,8]

Immune-mediated bone loss is likely driven by the stimulation of osteoclast differentiation, with activated Th17 cells being the only T cell with a net osteoclastogenic cytokine profile.[9,10] The Th17-produced cytokine, IL-17, promotes cartilage degradation and suppression of its synthesis,[11,12] as well as playing an important role in the pathogenesis of autoimmune diseases, such as RA.[13,14] Studies comparing CD4+ T cell profiles in the synovium of RA and OA patients have shown an increased amount of IL-17 compared to healthy controls but to a lesser degree in OA patients.[15,16]

Both the tuberculin skin test (TST) post-Bacille Calmette–Guérin (BCG) vaccination and immune-mediated bone loss are driven by some of the same immunological pathways. The TST reaction is dependent on CD4 Th1 lymphocytes, macrophages, and monocytes,[17] but, following the characterization of Th17 cells,[18] it has been shown that Th17 activity is important to establish the post-BCG vaccination response,[19,20] as well as that a lack of the Th17-specific cytokine IL-17 inhibits the delayed-type hypersensitivity response measured by TST.[21]

Between 1948 and 1975, Norway implemented a mandatory mass tuberculosis screening program, which was preceded by the introduction of a school vaccination program with the BCG vaccine for children aged 12–14 years old.[22,23] During the screening program, approximately 80% of the eligible adult Norwegian population were screened in repetitive rounds with chest X-ray, TST, and documentation of BCG vaccination. Nonvaccinated individuals who had a negative TST were offered a BCG vaccination.[24] We have previously shown an association between TST and the risk of hip fracture later in life.[25] This standardized manner of vaccination and measurement of postvaccination responses in a population-based cohort presents a unique opportunity to investigate immune system variation and its relation to bone-related outcomes since there are shared immunological pathways between the postvaccination responses, immune-mediated bone loss, and cartilage degradation.

Given the shared underlying immunological pathway, particularly Th17-mediated pathways, TST measurements following BCG vaccination could be studied as a surrogate marker of the immune responses that are believed to induce cartilage degradation and bone loss. The main aim of the current study was to explore a potential relationship between these immune responses and the subsequent risk of hip OA and total hip arthroplasty (THA). THAs recorded by the Norwegian Arthroplasty Register (NAR) were used as endpoints. We hypothesized that a positive TST after BCG vaccination is associated with an increased risk of requiring a THA due to OA or RA later in life.

Methods

Study population

The Norwegian national mass mandatory tuberculosis screening program was conducted between 1943 and 1975 and aimed to reduce the risk of tuberculosis infection in the general population. It covered 18 of 19 counties and included X-ray examination, height, and weight measurement, TST measurement, and BCG vaccination by indication. TST-negative individuals younger than 50 years old received BCG vaccination.[23] Computerized records from the screening program are available from 1963 and onward and include 1 911 599 individuals. BCG vaccination was gradually implemented in the Norwegian School vaccination program starting in 1947 and achieved high coverage during the 1950s. All children between 12 and 14 years were offered the vaccine.[23]

The study population was selected to have the recorded TST reflect prior BCG vaccination rather than exposure to tuberculosis infection. We, therefore, included individuals born between 1940 and 1960 (517 664 individuals) that had received BCG vaccination between 12 and 20 years of age at least 1 year prior to TST examination (258 580 individuals). The majority of the included individuals had received their BCG vaccination during the school vaccination program (80%). Since the extended time between BCG and TST examination (around 15 years) may decrease the TST reactivity,[26] we further restricted our sample to those aged 14–30 at TST examination with a maximum time interval between BCG and TST of 15 years (242 918 individuals). We also excluded individuals who, for any reason, were referred for further evaluation due to findings on the chest X-ray (1119 individuals). The final study population included 236 770 individuals who were alive and living in Norway at the start of the follow-up on September 15, 1987 (Fig. 1).

Tuberculin skin test

The national mass mandatory tuberculosis screening used adrenaline Pirquet as TST. Adrenalin was added to the Norwegian-produced synthetic tuberculin medium, and two drops of tuberculin solution were placed below the elbow on the volar side. A 5 mm subcutaneous scratch was performed through each of the drops, and the largest induration site was read 48–72 h later[27]. TST was defined and grouped according to strict national guidelines: negative (< 4 mm) and positive (≥4 mm). Strong positive reactions were usually defined as reactions of ≥8 mm.[28]

Outcome—THA

The NAR was established in 1987, and by 1991, all hospitals in Norway performing THAs included patients. In 1994, it expanded to include all kinds of arthroplasties. The register collects information on patient identification, the reason for and type of operation, date of surgery, sex, and physical status according to the American Society of Anesthesiologists (ASA) classification system, which is reported by the surgeon through a performed questionnaire.[29] The data have been validated against data in the Norwegian Patient Register for the period 2017–2018 and showed 97.5% completeness of reporting of primary THAs and nearly 100% coverage of Norwegian hospitals.[4]

The current study included data on primary THA due to OA or RA from September 15, 1987, to September 2020. Only the first THA during follow-up for each individual was considered.

Statistics Norway provided information on dates of death and emigration. All three databases were linked on a person-level linkage. Individuals were followed from September 15, 1987, to either receiving their first THA for OA or RA (outcomes) or censoring due to THA for other causes, emigration, death, or end of the follow-up on September 30, 2020, whichever occurred first.

Statistical methods

For data analysis, we used STATA version SE 16.1 (StataCorp, College Station, TX). Characteristics of participants who did and did not receive THA were compared using two-sample *T*-tests and chi-square tests for continuous and categorical variables, respectively. Hazard ratios (HRs) with 95% confidence intervals (CIs) for THA according to TST results were obtained using a multivariable Cox proportional hazard model with time since the start of follow-up (days) as timescale. The Cox model included the following covariates: age at BCG vaccination (years), the time between BCG vaccination and TST (years), the time between TST and the start of follow-up (years), BMI at the time of TST examination (categorical, < 18.5, < 25, < 30, and ≥30), and county (categorical). TST reactivity was both included as a categorical variable (< 4 mm, ≥4 mm, and ≥8 mm)

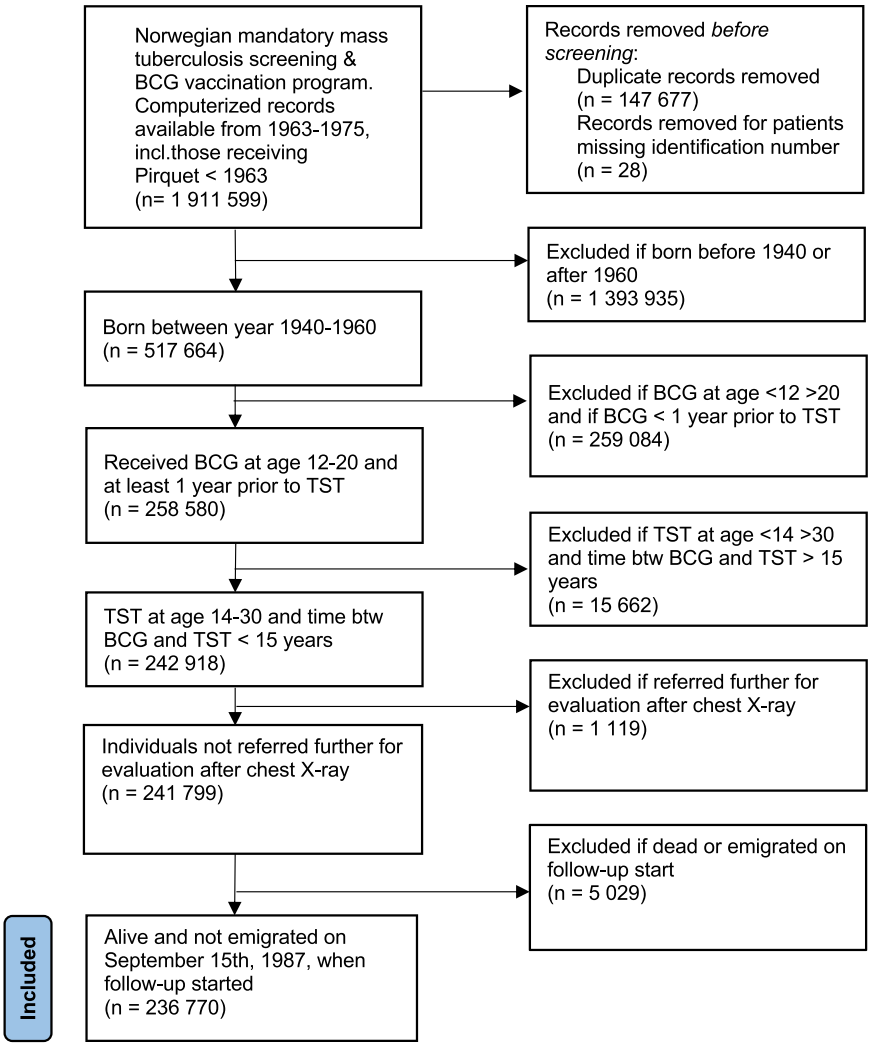

Fig. 1 Osteoarthritis and Cartilage

Study population.

and a continuous variable (4 mm increments) in the model. Tests of proportional hazards did not reveal any violations of the assumptions. Missing data were handled with a listwise deletion in the Cox model.

An earlier publication using similar data demonstrated an interaction effect between sex and TST ($p < 0.05$). This was, therefore, prespecified in our analyses, and the results are presented as sex-specific. All analyses were performed with either THA due to OA or THA due to RA as the outcome and presented separately. The exact proportion of individuals who satisfy the American College of Rheumatology classification criteria for OA was not provided but is expected to be high as strict clinical and radiologic findings (joint space narrowing < 2 mm, osteophytes, pain in the hip, and/or decreased range of motion) must be present to receive a THA.[30]

To further standardize the exposure and reduce the variation in TST size that is solely due to waning reactivity (rather than individual variation in immune reactivity), reduce information bias related to sampling techniques or indication, and limit age-related risk factors for gaining a THA, which may override the immunological effects, we performed three sensitivity analyses where we limited the study population to a) those who had received BCG vaccination between age 12 and 14 (likely school vaccination); b1) individuals receiving BCG at age 12–14, with a maximum time of 10 years between BCG vaccination and TST; and b2) sensitivity analysis b1 restricted to THA due to OA and censored at 70 years of age.

A *p-value* < 0.05 was considered statistically significant. The study was performed according to the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) statement.

Ethics

The study was approved by the regional ethics committee (REK Southeast, reference number 15538), the Norwegian Institute of Public Health, the Norwegian Directorate of Health, and the Norwegian Arthroplasty Registry and Statistics Norway. The research project has obtained exemption from confidentiality from the Regional Committee for Medical and Health Research Ethics based on the Norwegian Act on Medical and Health Research (the Health Research Act). The study complies with the General Data Protection

	Men (n = 116 524)	Women (n = 120 246)	Both sexes (n = 236 770)
Follow-up time, median years (IQR)	33.0 (33.0, 33.0)	33.0 (33.0, 33.0)	33.0 (33.0, 33.0)
Age at BCG, mean years (SD)	13.5 (1.9)	13.4 (1.7)	13.5 (1.8)
Age at TST, mean years (SD)	20.0 (4.1)	20.2 (4.1)	20.1 (4.1)
Time between BCG and TST, mean years (SD)	6.4 (3.9)	6.7 (3.9)	6.6 (3.9)
TST negative, N (%)	15 748 (13.5)	24 063 (20.0)	39 811 (16.8)
TST positive, N (%)	59 478 (51.0)	60 188 (50.1)	119 666 (50.5)
TST strong positive, N (%)	41 298 (35.4)	35 995 (29.9)	77 293 (32.7)
TST infiltrate size, mean mm (SD)	6.4 (2.7)	5.9 (2.8)	6.1 (2.8)
BMI, mean kg/m^2 (SD)*	22.1 (2.8)	21.9 (3.0)	22.0 (2.9)
Age at start of follow-up, mean years (SD)	38.4 (4.5)	38.6 (4.4)	38.5 (4.4)
Age at THA due to OA, mean years (SD)	65.0 (6.5)	65.6 (6.4)	65.4 (6.5)
Age at THA due to RA, mean years (SD)	59.4 (10.2)	60.8 (9.3)	60.5 (9.5)

*Only BMI had missing data, including 84 men and 222 women.

Table 1

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Characteristics of study population (n = 236 770).

Regulation, and a Data Protection Impact Assessment has been carried out in consultation with the Data Protection Officer at the Norwegian Institute of Public Health. The registration of data in the NAR was performed confidentially on patient consent and according to Norwegian and EU data protection rules.

Results

In the study population of 236 770 individuals, there were 116 524 (49%) men and 120 246 (51%) women. The mean age at BCG vaccination was 13.5 years (SD 1.8 years), and the mean time between BCG and TST measurement was 6.6 years (SD 3.9 years). The mean age at the start of follow-up was 38.5 years (SD 4.4 years) (Table 1).

There were 10 698 individuals who received a THA during follow-up, of which 10 394 (63% women) were due to OA and 304 (77% women) due to RA, with a median follow-up time of 26.2 years (Interquartile Range (IQR) 21.4; 29.6). The mean age at THA was 65.4 years (SD 6.4 years). Individuals who received a THA were slightly older at vaccination (13.7 years [SD 1.9 years] vs 13.5 years [SD 1.8 years], $p < 0.001$) and had extended time between BCG vaccination and TST measurement (7.7 years [SD 4.0 years] vs 6.5 years [SD 3.9 years], $p < 0.001$) and larger TSTs (6.2 mm [SD 2.8 mm] vs 6.1 mm [SD 2.8 mm], $p = 0.11$). Characteristics between patients with THA due to OA versus no THA and THA due to RA versus no THA are presented in Supplementary Tables 1 and 2.

There was no increased risk of THA due to OA among men with either a positive (HR = 1.01, 95% CI 0.92–1.12, and $p = 0.78$) or strong positive TST (HR = 1.06, 95% CI 0.95–1.18, and $p = 0.30$) compared to those with a negative TST. Among women, there was no increased risk with a positive TST (HR = 0.98, 95% CI 0.92–1.05, $p = 0.56$), but for women with a strong positive TST result, there was a 10% decreased risk (HR = 0.90, 95% CI 0.84–0.97, and $p < 0.01$) of THA due to OA compared to those with a negative TST (Table 2).

Men with a positive (HR = 1.76, 95% CI 0.74–4.16, and $p = 0.20$) or strong positive TST (HR = 1.43, 95% CI 0.57–3.58, and $p = 0.44$) had a nonsignificant trend of increased risk of THA due to RA compared to those with a negative TST. There was no association between positive (HR = 1.03, 95% CI 0.72–1.46, and $p = 0.88$) and strong positive TST (HR = 1.00, 95% CI 0.68–1.47, and $p = 1.00$) compared to negative TST and the risk of THA for RA in women (Table 3).

When entered as a continuous variable, TST was associated with similar results as in the other Cox models.

Sensitivity analysis

Restricting the main Cox model to those individuals that had most likely received BCG vaccination as part of the school vaccination program (12–14 years) yielded similar results as the overall analysis (Supplementary Tables 3 and 4).

To limit the chance of mycobacterial exposure, ensuring standardized BCG vaccination across the study population, and reducing potential changes in TST results due to increased time between BCG and TST, the model was further restricted to those who received BCG vaccination at age 12–14 and had a maximum time between BCG and TST of 10 years. This yielded a 14% nonsignificantly increased risk of hip arthroplasty due to OA among men with a strong positive TST (HR = 1.14, 95% CI 0.99–1.31, and $p = 0.07$) compared to negative TST. In women, the earlier observed reduced risk for THA in the strong positive TST group due to OA was now no longer statistically significant. There was no change in risk estimates for THA due to RA in men or women (Supplementary Tables 5 and 6).

When individuals in the OA group in the most restricted sensitivity analysis were censored at 70 years of age, slightly larger risk estimates were observed in men, with a p-value trending to become statistically significant (HR = 1.14, 95% CI 0.99–1.31, and $p = 0.07$) for positive TST and (HR = 1.16, 95% CI 1.00–1.36, and $p = 0.05$) for strong positive TST compared to negative TST. There was no change in risk estimates in women, but when TST was entered as a continuous variable, the effect estimate became statistically significant (HR = 0.94, 95% CI 0.91–0.98, and $p < 0.01$) (Supplementary Table 7).

Discussion

Results of our main analysis showed a decreased risk of THA due to OA among women with a strong positive TST compared with a negative TST and no risk change among men. When we further standardized the exposure, by restricting age at vaccination and time until measurement of TST, there was a statistically nonsignificant increased risk of THA among men with a strong positive TST and no difference in risk between TST groups among women. None of the analyses regarding THA due to RA among men or women revealed any significant difference in risk between the TST groups although there was a nonsignificant trend of increased risk among men. We hypothesized that restricting the study population to those receiving a THA at a younger age would more clearly reflect a potential immunological impact since other much more impactful risk factors for

	Men						Women					
	n (%)	THA (%)	Age-adjusted HR*	Fully-adjusted HR**	*p*-Value	95% CI	n (%)	THA (%)	Age-adjusted HR*	Fully-adjusted HR**	*p*-Value	95% CI
Tuberculin skin test (TST)												
Negative, ref: (< 4 mm)	15 733 (13.5)	465 (12.1)	1.00	1.00	(Ref.)	(Ref.)	24 027 (20.0)	1 303 (19.9)	1.00	1.00	(Ref.)	(Ref.)
Positive (4–7 mm)	59 429 (51.0)	1 867 (48.8)	1.02	1.01	0.78	0.92–1.12	60 075 (50.1)	3 292 (50.1)	1.00	0.98	0.56	0.92–1.05
Strong positive (≥8 mm)	41 264 (35.4)	1 497 (39.1)	1.08	1.06	0.30	0.95–1.18	35 917 (29.9)	1 970 (30.0)	0.94	0.90	< 0.01	0.84–0.97
HR per 4 mm increase in infiltrate size				1.03	0.27	0.98–1.08				0.95	< 0.01	0.92–0.98

*Estimated using a Cox regression model adjusted for age at follow-up start (years).
**Estimated using a Cox regression model adjusted for the following covariates: age at BCG (years), time between BCG and TST (years), time between TST and follow-up start (years), BMI (categorical), and county (categorical).

Table 2

Hazard ratios for THA due to OA by TST results divided into groups by sex.

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	Men						Women					
	n (%)	THA (%)	Age-adjusted HR*	Fully-adjusted HR**	*p*-Value	95% CI	n (%)	THA (%)	Age-adjusted HR*	Fully-adjusted HR**	*p*-Value	95% CI
Tuberculin skin test (TST)												
Negative, ref: (< 4 mm)	15 733 (13.5)	6 (8.6)	1.00	1.00	(Ref.)	(Ref.)	24 027 (20.0)	44 (18.4)	1.00	1.00	(Ref.)	(Ref.)
Positive (4–7 mm)	59 429 (51.0)	41 (58.6)	1.77	1.76	0.20	0.74–4.16	60 075 (50.1)	118 (50.4)	1.06	1.03	0.88	0.72–1.46
Strong positive (≥8 mm)	41 264 (35.4)	23 (32.9)	1.37	1.43	0.44	0.57–3.58	35 917 (29.9)	72 (30.8)	1.04	1.00	1.00	0.68–1.47
HR per 4 mm increase in infiltrate size				1.04	0.82	0.73–1.50				0.99	0.90	0.82–1.19

*Estimated using a Cox regression model adjusted for age at follow-up start (years).
**Estimated using a Cox regression model adjusted for the following covariates: age at BCG (years), time between BCG and TST (years), time between TST and follow-up start (years), BMI (categorical), and county (categorical).

Table 3

Hazard ratios for THA due to RA by TST results divided in groups by sex.

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receiving a THA, such as comorbidity, medication, biological turnover, and hormonal changes, become highly prevalent with increasing age. A further sensitivity analysis that restricted follow-up to 70 years of age was, therefore, performed, which yielded somewhat stronger risk estimates for men.

In our analysis, TST reactivity following BCG vaccination was used as a measure of individual variation in immune activity, but there are several external factors that could confound this. First, TST reactivity is dependent on the age at vaccination and the time between BCG and TST. For those vaccinated during infancy, it has consistently been shown to wane rapidly within 1 year, while this can take more than 10–15 years for those vaccinated during young adulthood.[26,31–34] Second, while the prevalence of TB infections decreased drastically during the first half of the 20th century, nontuberculous mycobacteria may also influence TST reactivity although infections with these are primarily tied to immunocompromised individuals.[35,36] By limiting the age range of the study population at both the time of vaccination and the time of TST measurement, it is more likely that the included individuals were vaccinated and tested in a similar manner as part of the school vaccination program and the tuberculosis screening program, and the TST reactivity reflects the vaccination rather than any individual underlying illness. This could potentially explain why the largest effect estimates for OA men only were present in the further restricted sensitivity analysis, where the TST reactivity is even more likely to represent individual variation in immune responses.

We hypothesized that an increased TST reactivity would be associated with an increased risk of THA later in life, but this was only suggested in men having OA. Among women with OA, there was, on the contrary, a slightly reduced risk among those with an increased reactivity. One explanation for this difference could be the sex-dependent immune responses toward tuberculin, which have previously been described and shown that men generally have a stronger reaction to tuberculin compared to women,[37,38] and the Th1 responses that are crucial to the TST are stimulated by androgens rather than estrogen.[39] The female reproductive system and sex hormones will also have an impact on the immune system, which, to a much larger degree, varies throughout life, with, for example, pregnancy and menopause.[39] It is, therefore, likely that these measured TST responses at a young age represent somewhat different underlying pathways and individual variations among men than what they do for women.

RA is an autoimmune disease that is Th1- and Th17-dependent,[40] with higher amounts of Th17 being found in the synovium of patients with RA compared to patients with OA.[41,42] Since both cells are involved in the TST reactivity, we expected a stronger association between TST results and THA caused by RA than by OA. This was partly the case, with RA having higher effect estimates than OA, but we cannot conclude from our analysis given the low number of events and wide 95% CIs.

To our knowledge, this is the first population-based study to investigate the association between individual postvaccination immune response and the risk of THA. Our findings in the OA group are in accordance with the previous finding of a 20%–25% increased risk of hip fracture in men with a positive or strong positive TST, respectively, with a slight protective association among women in a sensitivity analysis.[25] As Th17 cells are known to be osteoclastogenic, and inhibiting osteoclasts both reduces cartilage and bone degradation,[43] we expected TST reactivity to be associated with an increased risk of THA due to OA. However, it is important to emphasize that the TST reactivity following BCG vaccination does not precisely reflect either isolated Th1 or Th17 activity, and the exact involvement of these immune pathways in the development of OA remains to be fully elucidated.

Strengths of this study include its population-wide design with 33 years of follow-up regarding THA, using nationwide data from health studies and registries that cover the population of Norway. Norway has universal public healthcare and administrative registries that enable individual-level linkage based on the personal identification number of each inhabitant. The mass tuberculosis screening was mandatory and covered approximately 80% of the eligible adult population, and the coverage and completeness of the NAR are 97.5% for primary THAs.[4] Individuals in our study population received a THA at a younger age, with a mean age of 65.4 years, compared to the background population as a whole, with a mean age of 67–69 years. This was a consequence of the studies' birth year restrictions, limiting the risk of including individuals exposed to TB bacteria, simultaneously avoiding a larger proportion of THAs at a more advanced age that would likely introduce a number of more prevalent risk factors for THA that could influence and mask the immunological effect that we are studying.

There are some limitations to this study. First, as already discussed, measuring TST alone can only account for some of the immune pathways involved in OA and RA development, and other cascades are not considered here. TST was measured at a single time point, and other health and lifestyle-related factors can have made a large impact on the risk of receiving a THA in the intervening decades. Second, since the collection of THA data did not start until 1987, it is likely that some THAs in the study population were not captured. However, given that the maximum age of our study population was 47 years old in 1987, THAs prior to 1987 would have had to occur at a very young age and are, therefore, likely to comprise a small number of individuals with RA. New treatment options for RA, particularly immunosuppressant drugs, have also reduced the use of THA among these individuals during the study period, resulting in a change in risk during follow-up.[44] Third, we did not adjust for the confounding role of socioeconomic status (SES), occupation, physical activity, and comorbidities. SES can have a confounding role, although exposure was generally measured during adolescence. It has been shown that low SES was associated with an increased risk of exposure to tuberculosis,[45,46] which again will have influenced the exposure, and low SES is also associated with an increased risk of THA.[47] We have included the county as a confounder in our analysis, which accounts for some of the potential variations in SES, but data on SES were not available to us. Regarding the remaining covariates listed, we find it more likely that these factors rather act as mediators in our analysis since they did not precede the exposure (postvaccination tuberculin response) and would not be considered to have influenced it even though they may be strongly related to the outcome. They have, therefore, not been adjusted for. Another limitation is that we cannot be certain that all the patients gaining a THA satisfied the American College of Rheumatology classification criteria, but we assume that most of Norwegian orthopedic surgeons accept individuals for surgery according to strict clinical and radiographic criteria.

In summary, data from our population-based cohort study showed a slightly decreased risk of THA due to OA in women with an increased postvaccination immune response and increased risk estimates among men, which is consistent with previous publications. However, the effect among men was not statistically significant, although the risk estimates increased when the exposure was further standardized. In these restricted subsamples, the reduced risk among women was no longer statistically significant. Censoring the study population at 70 years of age resulted in even larger risk estimates trending toward statistical significance for men, which highlights how these immunological factors are likely masked by other more impactful age-dependent risk factors later in life. Further research is needed to draw any definitive conclusions regarding the

topic in question, and we encourage future studies to also include data on other joints, such as knee arthroplasties, to assess if the observed trends are isolated to hip arthroplasties or not.

Author contributions

Study conception and design: SR, JD, LN, MW, and HEM. Acquisition of data: KH, OF, and AMF. Analysis and interpretation of data: SR, JD, HEM, and KH. Drafting the article: SR and JD. Critical revision and final approval of the article: SR, JD, LN, MW, HEM, KH, OF, and AMF.

SR (sonroj@ous-hf.no) and JD (jesper.dahl@fhi.no) take responsibility for the integrity of the work as a whole, from the inception of the study to the finished article.

Role of the funding source

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Competing interest statement

None of the authors declare any conflict of interest.

Access to data

Due to legal restrictions, this composite data set cannot be made publicly available. However, the data may be available on request to the different data owners (Norwegian Institute of Public Health, The Norwegian Arthroplasty Register, and Statistics Norway).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2023.05.007.

References

1. Abramoff B, Caldera FE. Osteoarthritis: Pathology, diagnosis, and treatment options. Med Clin North Am 2020;104(2):293–311.
2. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Engeland A, Meyer HE. The impact of body mass index on later total hip arthroplasty for primary osteoarthritis: A cohort study in 1.2 million persons. Arthritis Rheum 2006;54(3):802–7.
3. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Meyer HE. Risk factors for total hip replacement due to primary osteoarthritis: A cohort study in 50,034 persons. Arthritis Rheum 2002;46(3):675–82.
4. Furnes O, Hallan G, Kroken G, Fenstad AM. Årsrapport for 2019 med plan for forbedringstiltak Nasjonalt register for leddproteser; 2020. Available from: 〈https://www.kvalitetsregistre.no/sites/default/files/25_arsrapport_2019_nasjonalt_leddproteseregister.pdf〉 .
5. Li YS, Luo W, Zhu SA, Lei GH. T cells in osteoarthritis: Alterations and beyond. Front Immunol 2017;8:356.
6. Nees TA, Rosshirt N, Zhang JA, Platzer H, Sorbi R, Tripel E, *et al*. T helper cell infiltration in osteoarthritis-related knee pain and disability. J Clin Med 2020;9(8).
7. Berenbaum F, Walker C. Osteoarthritis and inflammation: A serious disease with overlapping phenotypic patterns. Postgrad Med 2020;132(4):377–84.
8. Dar HY, Azam Z, Anupam R, Mondal RK, Srivastava RK. Osteoimmunology: The Nexus between bone and immune system. Front Biosci 2018;23:464–92.
9. Takayanagi H. Osteoimmunology and the effects of the immune system on bone. Nat Rev Rheumatol 2009;5(12):667–76.
10. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, *et al*. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med 2006;203(12):2673–82.
11. Chabaud M, Lubberts E, Joosten L, van Den Berg W, Miossec P. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. Arthritis Res 2001;3(3):168–77.
12. Cai L, Yin JP, Starovasnik MA, Hogue DA, Hillan KJ, Mort JS, *et al*. Pathways by which interleukin 17 induces articular cartilage breakdown in vitro and in vivo. Cytokine 2001;16(1):10–21.
13. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: From mechanisms to therapeutic testing. Nat Rev Immunol 2014;14(9):585–600.
14. Tabarkiewicz J, Pogoda K, Karczmarczyk A, Pozarowski P, Giannopoulos K. The role of IL-17 and Th17 lymphocytes in autoimmune diseases. Arch Immunol Ther Exp 2015;63(6):435–49.
15. Chabaud M, Durand JM, Buchs N, Fossiez F, Page G, Frappart L, *et al*. Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. Arthritis Rheum 1999;42(5):963–70.
16. Hussein MR, Fathi NA, El-Din AM, Hassan HI, Abdullah F, Al-Hakeem E, *et al*. Alterations of the CD4(+), CD8(+) T cell subsets, interleukins-1beta, IL-10, IL-17, tumor necrosis factor-alpha and soluble intercellular adhesion molecule-1 in rheumatoid arthritis and osteoarthritis: preliminary observations. Pathol Oncol Res 2008;14(3):321–8.
17. Black CA. Delayed type hypersensitivity: Current theories with an historic perspective. Dermatol Online J 1999;5(1):7.
18. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, *et al*. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 2005;6(11):1133–41.
19. Gopal R, Lin Y, Obermajer N, Slight S, Nuthalapati N, Ahmed M, *et al*. IL-23-dependent IL-17 drives Th1-cell responses following Mycobacterium bovis BCG vaccination. Eur J Immunol 2012;42(2):364–73.
20. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cilley GE, *et al*. IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during *Mycobacterium tuberculosis* challenge. Nat Immunol 2007;8(4):369–77.
21. Umemura M, Yahagi A, Hamada S, Begum MD, Watanabe H, Kawakami K, *et al*. IL-17-mediated regulation of innate and acquired immune response against pulmonary Mycobacterium bovis bacille Calmette-Guerin infection. J Immunol 2007;178(6):3786–96.
22. Nokleby H, Feiring B. The Norwegian vaccination program. Tidsskr Nor Laegeforen 2006;126(19):2538–40.
23. Folkehelseinstituttet. Barnevaksinasjonsprogrammet-veileder for helsepersonell; 2008. Available from: 〈https://www.fhi.no/nettpub/vaksinasjonsveiledere-for-helsepersonell/vaksinasjon/barnevaksinasjonsprogrammet/〉 .
24. Bjartveit K. Mass miniature radiography in Norway, today and in the future. Scand J Respir Dis Suppl 1972;80:31–42.
25. Dahl J, Holvik K, Heldal E, Grimnes G, Hoff M, Finnes TE, *et al*. Individual variation in adaptive immune responses and risk of hip fracture-A NOREPOS population-based cohort study. J Bone Miner Res 2020;35(12):2327–34.
26. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guerin

vaccination on tuberculin skin test measurements. Thorax 2002;57(9):804–9.
27. Jentoft HF, Omenaas E, Eide GE, Gulsvik A. Tuberculin test variability: Using the Norwegian Adrenaline-Pirquet method. Int J Tuberc Lung Dis 1999;3(4):326–9.
28. Bjartveit K., Eilertsen E, Heldal E, Sandven P, Øvreberg K, editors. Control of Tuberculosis. Manual for the community health service; 1996. page 97, Available from https://www.nb.no/items/a7b6a095b38d54f55f51f7876d3fe2eb?page=97&searchText=bjartveit%20tuberkulose.
29. Havelin LI, Espehaug B, Vollset SE, Engesaeter LB, Langeland N. The Norwegian arthroplasty register. A survey of 17,444 hip replacements 1987-1990. Acta Orthop Scand 1993;64(3):245–51.
30. Pedersen A, Johnsen S, Overgaard S, Soballe K, Sorensen HT, Lucht U. Registration in the danish hip arthroplasty registry: Completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. Acta Orthop Scand 2004;75(4):434–41.
31. Menzies D. What does tuberculin reactivity after bacille Calmette-Guerin vaccination tell us? Clin Infect Dis 2000;31(Suppl 3):S71–4.
32. Mancuso JD, Mody RM, Olsen CH, Harrison LH, Santosham M, Aronson NE. The long-term effect of Bacille Calmette-Guerin vaccination on Tuberculin skin testing: A 55-year follow-up study. Chest 2017;152(2):282–94.
33. Karalliedde S, Katugaha LP, Uragoda CG. Tuberculin response of Sri Lankan children after BCG vaccination at birth. Tubercle 1987;68(1):33–8.
34. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: What is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis 2006;10(11):1192–204.
35. Folkehelseinstituttet. Tuberculosis-manual for healthcare workers; 2010 [updated 19.06.2010]. Available from: 〈https://www.fhi.no/nettpub/smittevernveilederen/sykdommer-a-a/tuberkulose/〉 .
36. Monteiro NF, Peres S, Mansinho K. Non-Tuberculous Mycobacteria: Seven-year experience of a tertiary hospital. Acta Med Port 2019;32(3):208–13.
37. Diwan VK, Thorson A. Sex, gender, and tuberculosis. Lancet 1999;353(9157):1000–1.
38. Shaaban MA, Abdul Ati M, Bahr GM, Standford JL, Lockwood DN, McManus IC. Revaccination with BCG: Its effects on skin tests in Kuwaiti senior school children. Eur Respir J 1990;3(2):187–91.
39. Giefing-Kroll C, Berger P, Lepperdinger G, Grubeck-Loebenstein B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. Aging Cell 2015;14(3):309–21.
40. Leipe J, Pirronello F, Schulze-Koops H, Skapenko A. Altered T cell plasticity favours Th17 cells in early arthritis. Rheumatol 2020;59(10):2754–63.
41. Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, *et al.* Role of the IL-23/IL-17 pathway in rheumatic diseases: An overview. Front Immunol 2021;12, 637829.
42. Penatti A, Facciotti F, De Matteis R, Larghi P, Paroni M, Murgo A, *et al.* Differences in serum and synovial CD4+ T cells and cytokine profiles to stratify patients with inflammatory osteoarthritis and rheumatoid arthritis. Arthritis Res Ther 2017;19(1):103.
43. Strassle BW, Mark L, Leventhal L, Piesla MJ, Jian Li X, Kennedy JD, *et al.* Inhibition of osteoclasts prevents cartilage loss and pain in a rat model of degenerative joint disease. Osteoarthr Cartil 2010;18(10):1319–28.
44. Taylor-Williams O, Nossent J, Inderjeeth CA. Incidence and complication rates for total hip arthroplasty in rheumatoid arthritis: A systematic review and meta-analysis across four decades. Rheumatol Ther 2020;7(4):685–702.
45. Nana Yakam A, Noeske J, Dambach P, Bowong S, Fono LA, Ngatchou-Wandji J. Spatial analysis of tuberculosis in Douala, Cameroon: Clustering and links with socio-economic status. Int J Tuberc Lung Dis 2014;18(3):292–7.
46. Oren E, Koepsell T, Leroux BG, Mayer J. Area-based socio-economic disadvantage and tuberculosis incidence. Int J Tuberc Lung Dis 2012;16(7):880–5.
47. Edwards NM, Varnum C, Overgaard S, Pedersen AB. The impact of socioeconomic status on the utilization of total hip arthroplasty during 1995-2017: 104,055 THA cases and 520,275 population controls from national databases in Denmark. Acta Orthop 2021;92(1):29–35.