Adiposity and Physical Activity as Risk Factors for Developing Psoriatic Arthritis: Longitudinal Data From a Population-Based Study in Norway

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Objective. Adiposity is prevalent among patients with psoriatic arthritis (PsA). However, the temporal relation is unclear. The present study was undertaken to investigate whether adiposity and body fat distribution are related to the risk of developing PsA, and whether physical activity could modify the possible risk.

Methods. We included 36,626 women and men from the Norwegian Nord-Trøndelag Health Study without diagnosed PsA at baseline from 1995 to 1997. Cox regression analysis was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) of incident PsA at follow-up from 2006 to 2008.

Results. During follow-up, 185 new cases of PsA were reported. Increases of 1 SD in body mass index (BMI) (4.2 and 3.5 kg/m² for women and men, respectively) and waist circumference (10.8 and 8.6 cm, respectively) were associated with HRs of 1.40 (95% CI 1.24, 1.58) and 1.48 (95% CI 1.31, 1.68), respectively. Compared to individuals of normal weight, obese individuals had an HR of 2.46 (95% CI 1.65, 3.68), and overweight individuals had an HR of 1.41 (95% CI 1.00, 1.99). Comparing extreme quartiles of waist circumference yielded an HR of 2.63 (95% CI 1.73, 3.99). In analyses of combined effects using a BMI of <25 kg/m² and high physical activity as reference, a BMI of ≥25 kg/m² was associated with HRs of 2.06 (95% CI 1.18, 3.58) and 1.53 (95% CI 0.80, 2.91) among those with low and high physical activity levels, respectively. Corresponding HRs for high waist circumference and physical activity were 2.25 (95% CI 1.40, 1.63) and 1.85 (95% CI 0.95, 3.50).

Conclusion. The results suggest that adiposity, particularly central obesity, is associated with increased risk of incident PsA. Although there was no clear modifying effect of physical activity, high levels of physical activity reduced the risk of PsA, regardless of BMI.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. The observed prevalence varies from <0.01% to 0.67% in different countries (1–3), with the highest prevalence found in Norway (3). PsA is associated with obesity, dyslipidemia, and insulin resistance, all part of metabolic syndrome, and which significantly increase patients’ risk of cardiovascular disease (CVD) and mortality (4–8). In addition, obesity can reduce the treatment effect of disease-modifying medication (9). Compared to patients with psoriasis alone, the body fat percentage seems to be even higher in patients with PsA (10,11). Some authors claim that obesity is a consequence of psoriasis and PsA because of social isolation, depression, physical inactivity, high-fat diet, and alcohol consumption (11). Conversely, other studies indicate that high body mass index (BMI) is a cause of PsA rather than a consequence (12–14), and that even at a young age, obesity seems to increase the risk of PsA (15).

Adiposity might be an environmental trigger of PsA in genetically susceptible individuals (13,16). The adipose tissue is an...
endocrine organ producing inflammatory mediators, such as several different adipokines, which influence the pathophysiology of both CVD and inflammatory conditions, as seen in psoriatic diseases (17,18).

There is evidence that physical activity has the ability to modify the detrimental effects of adiposity on CVD and metabolic diseases (19–22). Moreover, high physical activity level can reduce body fat (23) and increase cardiorespiratory fitness (24), and both these factors are associated with a reduced risk of CVD (25). It is unknown whether physical activity can affect the ultimate development of PsA in genetically susceptible individuals. A potential concern is that physical trauma from vigorous exercise causing mechanical stress could potentially trigger an inflammatory response, such as enthesitis, thereby contributing to the development of PsA. There is some evidence that such local inflammatory responses may be of etiologic relevance to PsA, which has led to PsA being considered more of an autoinflammatory condition rather than a strictly autoimmune disease (26–28).

The aim of this longitudinal, population-based study was to investigate the association of adiposity and body fat distribution with the risk of developing PsA. Further, we examined whether a high physical activity level could modify the possible adverse effect of high BMI and waist circumference on the risk of incident PsA.

**MATERIALS AND METHODS**

**Study population.** This is a prospective study using data from the Nord-Trøndelag Health Study (HUNT); a population-based, longitudinal study conducted in Norway. HUNT consists of 3 consecutive surveys: HUNT1 (1986–1988), HUNT2 (1995–1997), and HUNT3 (2006–2008). All individuals ≥20 years of age were invited to participate, completing a comprehensive questionnaire and undergoing a clinical examination (29).

This study utilizes data from HUNT2 and HUNT3; the participation rate of the invited individuals was 70% of 93,898 in HUNT2, and 54% of 93,860 in HUNT3. Of 116,043 participants, 37,070 individuals participated in both surveys and were selected for this study.

For the purpose of the current study, we excluded 94 participants with onset of PsA before participation in HUNT2, 151 with missing information on BMI, as well as 200 participants with a BMI of <18.5 kg/m². The latter group was excluded due to small numbers of patients as well as the possibility that the low weight might relate to some intercurrent comorbidity. This left 36,626 participants available for analyses of BMI (Figure 1). Analyses of waist circumference and physical activity included 36,595 and 34,834 individuals due to some missing data on these respective factors.

All participants signed written informed consent, and the study was approved by the Regional Committee for Ethics in Medical Research (REC 2010/2661). The study was conducted according to the Declaration of Helsinki.

**Outcome.** At follow-up in HUNT3 (2006–2008), all participants received a first questionnaire with the invitation. Based on answers to this questionnaire, individuals reporting psoriasis or 6 other specific disorders (e.g., CVD, diabetes mellitus [DM], or cancer) were also given a more detailed questionnaire for the specific disease. Each participant could only fill in 2 additional questionnaires, and CVD and DM were prioritized (3). In 2012, an experienced rheumatologist (MH) validated possible cases of PsA by examining hospital medical records using the Classification of Psoriatic Arthritis (CASPAR) criteria. A total of 1,238 possible cases were included in the validation study based on their questionnaire response: 1) self-reported psoriasis and rheumatoid arthritis or ankylosing spondylitis; 2) self-reported psoriasis and CVD; and 3) self-reported psoriasis and answering “yes” or “I do not know” to the question about PsA (3). A total of 338 validated cases of PsA were identified in the records.

In addition to cases of PsA occurring between baseline (HUNT2) and follow-up in HUNT3, new cases of PsA diagnosed according to the hospital records between the follow-up survey in 2006–2008 and 2012 were also included in the current study. Additional details of the validation study have been previously presented (3).

**Exposures.** BMI, waist circumference, and waist-to-hip ratio. Standardized measures of body height (to the nearest cm) and weight (to the nearest one-half kg) obtained at the clinical examination in HUNT2 were used to calculate BMI (kg/m²) (30). Participants were then classified into 1 of 3 BMI categories according to the cutoff points suggested by the World Health Organization (WHO): normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25.0–29.9 kg/m²), or obese (BMI ≥30.0 kg/m²) (31).
For analysis of the combined effect of BMI, overweight and obesity were collapsed into 1 category (i.e., ±25 kg/m²).

Waist circumference was measured with a steel band to the nearest cm at the level of the umbilicus (30). Based on the distribution of the measures, participants were classified into 4 categories using the sex-specific quartiles as cutoffs (<74, 74–79, 80–87, and >87 cm in women; <87, 87–90, 91–96, and >96 cm in men). For analysis of the combined effect of waist circumference and BMI, waist circumference was split into 2 categories (± median value). Participants were also classified into 2 categories of waist circumference according to the sex-specific cutoff points suggested by the WHO: 1 = low (<81 cm in women, <95 cm in men), and 2 = high (≥81 cm in women, ≥95 cm in men) (32). This latter classification was used for the analysis of the combined effect of waist circumference and physical activity.

Hip circumference was measured with a steel band to the nearest cm at the thickest part of the hip. Waist-to-hip ratio was calculated as waist circumference (cm) divided by hip circumference (cm). Based on the distribution of the measures, participants were classified into 4 categories using the sex-specific quartiles as cutoffs (<0.75, 0.75–0.79, 0.80–0.82, and >0.82 cm in women; <0.86, 0.86–0.89, 0.90–0.92, and >0.92 cm in men). In addition, sex-specific SD scores (Z scores) were calculated for BMI, waist circumference, and waist-to-hip ratio as the observed value minus the sex-specific mean value, divided by the sex-specific SD. For individuals with information on body weight from HUNT1, the 10-year change in body weight from HUNT1 to HUNT2 was calculated by subtracting the weight at HUNT1 from the weight at HUNT2 and categorized into 4 groups.

**Physical activity.** Leisure-time physical activity was assessed using the following question: “How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time).” The participants were then asked to specify number of hours per week of light (no sweating or heavy breathing) and/or hard (sweating and heavy breathing) physical activity with the

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**Figure 1.** Flow chart of selection of study participants. BMI = body mass index; HUNT = Nord-Trøndelag Health Study; PsA = psoriatic arthritis.
response options: "none," "less than 1 hour," "1–2 hours," and "3 or more hours" for both light and hard activity (33). Based on this information, a new variable with 4 categories was constructed combining information on light and hard activity: inactive (no light or no hard activity); low activity (<3 hours of light and no hard activity); moderate activity (≥3 hours of light and/or <1 hour of hard activity); and high activity (any light and ≥1 hour of hard activity) (34). For the analyses of the combined effect, the 3 first categories (inactive, low activity, and moderate activity) were collapsed into 1 category.

**Statistical analysis.** Descriptive data are given as mean ± SD for continuous data and number (%) for categorical data. Cox regression analysis was used to calculate hazard ratios (HRs) of incident PsA associated with categories of baseline BMI, waist circumference, waist-to-hip ratio, and physical activity, as well as with continuous measures of these factors using both the original scale and sex-specific normalized values (Z score). Precision of the estimated associations was assessed with a 95% confidence interval (95% CI). Potential confounders were selected a priori based on knowledge about factors that could be associated with both the outcome and the exposures. All estimates were adjusted for possible confounding by age (as the time scale in the model), sex (female, male), smoking (current, former, never, unknown [3.9%]), and education (<10 years [elementary school], 10–12 years [high school], ≥13 years [college/university], and unknown [1.4%]). Due to uncertainty about the direction of possible confounding effects between BMI and physical activity, as well as waist circumference and physical activity, these factors were mutually adjusted in a supplementary analysis.

Similarly, the combined effects of BMI and physical activity, of waist circumference and physical activity, and of BMI and waist circumference on risk of PsA were estimated. In the first combined analysis, normal BMI and high physical activity level constituted the reference group. In the second analysis, low waist circumference according to WHO cutoffs and high physical activity level constituted the reference group. In the third analysis, normal BMI and waist circumference below median was the reference group.

The within-category median value of BMI and/or waist circumference was calculated for all the combined analyses.

Potential effect modification between the variables was assessed both as departure from additive effects, calculating the relative excess risk due to interaction (RERI), and as departure from multiplicative effects in a likelihood ratio test of a product term in the regression model. RERI estimates were calculated with 95% CIs using the following equation: \( RERI = RR_{11} - RR_{10} - RR_{01} + 1 \) (35), i.e., \( RERI > 0 \) indicates a synergistic effect beyond additivity.

In a sensitivity analysis, participants with a new onset of PsA within the first 3 years after HUNT2 were excluded to reduce possible reverse causality due to existing undiagnosed disease.

### Table 1. Characteristics of the population according to the 4 categories of physical activity at baseline*

| Category                  | Inactivity (n = 2,007) | Low activity (n = 10,742) | Moderate activity (n = 12,000) | High activity (n = 10,085) |
|---------------------------|------------------------|----------------------------|--------------------------------|---------------------------|
| Female                    | 965 (48.1)             | 6,802 (63.3)              | 6,743 (56.2)                   | 4,442 (44.0)              |
| Age, mean ± SD years      |                        |                            |                                |                           |
| Women                     | 47.7 ± 13.7            | 48.3 ± 12.7               | 46.8 ± 13.4                    | 43.1 ± 12.6               |
| Men                       | 27.3 ± 5.1             | 26.4 ± 4.4                | 25.8 ± 4.1                     | 25.1 ± 3.8               |
| BMI, mean ± SD kg/m²      |                        |                            |                                |                           |
| Women                     | 27.0 ± 3.9             | 26.8 ± 3.4                | 26.5 ± 3.2                     | 26.1 ± 3.0               |
| Men                       | 27.0 ± 3.9             | 26.8 ± 3.4                | 26.5 ± 3.2                     | 26.1 ± 3.0               |
| BMI, kg/m²                |                        |                            |                                |                           |
| 18.5–24.9                 | 712 (36.1)             | 3,960 (37.2)              | 4,925 (41.1)                   | 4,640 (46.4)              |
| 25.0–29.9                 | 817 (41.5)             | 4,856 (45.6)              | 5,375 (45.2)                   | 4,322 (43.2)              |
| ≥30.0                     | 441 (22.4)             | 1,828 (17.2)              | 1,596 (13.4)                   | 1,048 (10.5)              |
| Waist circumference, mean ± SD cm |                        |                            |                                |                           |
| Women                     | 84.1 ± 12.6            | 81.7 ± 10.9               | 79.7 ± 10.3                    | 77.3 ± 9.7               |
| Men                       | 93.2 ± 10.1            | 92.7 ± 8.8                | 91.6 ± 8.4                     | 89.6 ± 8.1               |
| Waist-to-hip ratio, mean ± SD |                        |                            |                                |                           |
| Women                     | 0.81 ± 0.06            | 0.80 ± 0.06               | 0.79 ± 0.06                    | 0.78 ± 0.05              |
| Men                       | 0.91 ± 0.06            | 0.90 ± 0.05               | 0.89 ± 0.05                    | 0.88 ± 0.05              |
| Education, years          |                        |                            |                                |                           |
| <10                       | 858 (42.8)             | 3,888 (36.2)              | 3,354 (28.0)                   | 1,886 (18.7)             |
| 10–12                     | 911 (45.4)             | 4,833 (45.0)              | 5,573 (46.4)                   | 4,987 (49.5)             |
| ≥13                       | 180 (9.0)              | 1,832 (17.1)              | 2,912 (24.3)                   | 3,128 (31.0)             |
| Smoking status            |                        |                            |                                |                           |
| Never                     | 697 (34.7)             | 4,319 (40.2)              | 5,139 (42.8)                   | 4,902 (48.6)             |
| Former                    | 540 (26.9)             | 2,897 (26.0)              | 3,383 (28.2)                   | 2,741 (27.2)             |
| Current                   | 708 (35.3)             | 3,092 (28.8)              | 3,031 (25.3)                   | 2,025 (20.1)             |
| Pain†                     |                        |                            |                                |                           |
| Yes                       | 1,082 (54.2)           | 5,542 (51.8)              | 5,481 (45.9)                   | 3,967 (39.5)             |

* Values are the number (%) unless indicated otherwise. BMI = body mass index.
† Pain and/or stiffness in muscle/skeleton in the last year.
at baseline. Assuming that the estimated associations reflect causal effects of high BMI and waist circumference on PsA risk, we estimated the population attributable fraction to quantify the proportion of PsA that potentially could be prevented by avoiding overweight and obesity.

Departure from the proportional hazards assumption was evaluated by tests of Schoenfeld residuals and by graphical inspection of log–log plots. All analyses were conducted using Stata for Windows, version 14.2.

RESULTS

A total of 36,626 participants were included in the study; 55% were women. A total of 185 incident cases (59% women) of PsA were diagnosed during follow-up; 164 between HUNT2 (1995–1997) and HUNT3 (2006–2008), and 21 between HUNT3 and 2012. The incidence proportion for 14 years was 0.5%. Table 1 displays baseline characteristics of the study population stratified by physical activity. There was no evidence of violation of the proportional hazards assumption for any of the results presented below.

Effect of BMI, waist circumference, and waist-to-hip ratio. An increase of 1 SD in BMI (4.2 kg/m² in women, and 3.5 kg/m² in men), waist circumference (10.8 cm in women, and 8.6 cm in men), and waist-to-hip ratio (0.06 in women, and 0.05 in men) was associated with adjusted HRs of 1.40 (95% CI 1.24, 1.58), 1.48 (95% CI 1.31, 1.68), and 1.39 (95% CI 1.24, 1.57) (Table 2). Individuals with a BMI of ≥30 kg/m² had an HR of 2.46 (95% CI 1.65, 3.68) compared to individuals of normal weight (BMI 18.5–24.9 kg/m²). Those in the highest quartile of waist circumference

| Table 2. Risk of incident psoriatic arthritis (PsA) during 14 years of follow-up associated with body mass index (BMI), waist circumference, waist-to-hip ratio, and leisure-time physical activity* |
|-----------------------------------------------|-----------------|------------------|-------------------|-----------------|
| **Person-years** | **No. of cases of incident PsA** | **Rate†** | **Crude HR (95% CI)‡** | **Adjusted HR (95% CI)§** |
| BMI, kg/m² | | | | |
| 18.5–24.9 | 230,376 | 59 | 2.6 | 1.00 (Ref.) | 1.00 (Ref.) |
| 25.0–29.9 | 252,561 | 79 | 3.1 | 1.33 (0.95, 1.87) | 1.41 (1.00, 1.99) |
| ≥30.0 | 82,884 | 43 | 5.2 | 2.33 (1.57, 3.47) | 2.46 (1.65, 3.68) |
| BMI per SD, kg/m²¶ | 565,820 | 181 | 3.2 | 1.39 (1.23, 1.57) | 1.40 (1.24, 1.58) |
| BMI per kg/m² | 565,820 | 181 | 3.2 | 1.09 (1.05, 1.12) | 1.09 (1.06, 1.12) |
| Waist circumference quartiles, cm# | | | | |
| First | 164,171 | 36 | 2.2 | 1.00 (Ref.) | 1.00 (Ref.) |
| Second | 126,933 | 36 | 2.8 | 1.36 (0.85, 2.16) | 1.35 (0.85, 2.14) |
| Third | 139,045 | 48 | 3.5 | 1.76 (1.14, 2.72) | 1.78 (1.15, 2.75) |
| Fourth | 135,176 | 63 | 4.7 | 2.60 (1.72, 3.95) | 2.63 (1.73, 3.99) |
| Waist circumference (WHO cutoffs) | | | | |
| Women <81 cm; men <95 cm | 351,084 | 94 | 2.7 | 1.00 (Ref.) | 1.00 (Ref.) |
| Women >80 cm; men >94 cm | 214,241 | 89 | 4.2 | 1.78 (1.33, 2.39) | 1.75 (1.30, 2.35) |
| Waist circumference per SD, cm** | 565,325 | 183 | 3.2 | 1.48 (1.31, 1.68) | 1.48 (1.31, 1.68) |
| Waist circumference, per cm | 565,325 | 183 | 3.2 | 1.03 (1.02, 1.04) | 1.04 (1.03, 1.05) |
| Waist-to-hip ratio, quartiles†† | | | | |
| First | 143,180 | 27 | 1.9 | 1.00 (Ref.) | 1.00 (Ref.) |
| Second | 140,277 | 44 | 3.1 | 1.70 (1.05, 2.75) | 1.64 (1.01, 2.65) |
| Third | 142,221 | 48 | 3.4 | 1.96 (1.22, 3.15) | 1.87 (1.16, 3.01) |
| Fourth | 139,648 | 64 | 4.6 | 2.95 (1.87, 4.66) | 2.74 (1.73, 4.34) |
| Waist-to-hip ratio, per SD‡‡ | 565,325 | 183 | 3.2 | 1.42 (1.26, 1.60) | 1.39 (1.24, 1.57) |
| Waist-to-hip ratio, per 0.1 unit | 565,325 | 183 | 3.2 | 1.36 (1.12, 1.65) | 1.78 (1.45, 2.19) |
| Physical activity | | | | |
| High | 155,892 | 41 | 2.6 | 1.00 (Ref.) | 1.00 (Ref.) |
| Moderate | 185,127 | 70 | 3.8 | 1.54 (1.05, 2.26) | 1.45 (0.98, 2.13) |
| Low | 165,915 | 54 | 3.3 | 1.33 (0.89, 2.01) | 1.22 (0.80, 1.84) |
| Inactive | 31,019 | 11 | 3.5 | 1.48 (0.76, 2.88) | 1.30 (0.66, 2.54) |

* 95% CI = 95% confidence interval; HR = hazard ratio; Ref. = reference; WHO = World Health Organization.
† Incidence of PsA per 10,000 person-years.
‡ Adjusted for age (as the time scale in the model).
§ Adjusted for sex, age, education level, and smoking status.
¶ Sex-specific SD: women, SD 4.2 kg/m²; men, SD 3.5 kg/m².
# Waist circumference quartiles: women (first ≤73 cm; second 74–79 cm; third 80–87 cm; fourth ≥88 cm); men (first ≤86 cm; second 87–90 cm; third 91–96 cm; fourth ≥97).
** Sex-specific SD: women, SD 10.8 cm; men, SD 8.6 cm.
†† Waist-to-hip ratio quartiles: women (first <0.75; second 0.75–0.79; third 0.80–0.82; fourth >0.82); men (first <0.86; second 0.86–0.89; third 0.90–0.92; fourth >0.92).
‡‡ Sex-specific SD: women, SD 0.06; men, SD 0.05.
had an HR of 2.63 (95% CI 1.73, 3.99) compared to those in the first quartile. Using WHO cutoffs, individuals with a high waist circumference (≥81 cm in women, ≥95 cm in men) had an HR of 1.75 (95% CI 1.30, 2.35) compared to those with a low waist circumference (WHO cutoffs: <81 cm in women, <95 cm in men). Correspondingly, individuals in the fourth sex-specific quartile of waist-to-hip ratio had an HR 2.74 (95% CI 1.73, 4.34) compared to the first quartile. In supplementary analysis of ~10 years weight change (data not shown), those who increased ≥10 kg had an HR of 1.41 (95% CI 0.86, 2.30) compared to those who were weight stable (±2.5 kg).

In analyses of the joint categories of waist circumference and BMI, individuals with a waist circumference greater than median had an HR of 2.13 (95% CI 1.49, 3.07) if BMI was ≥25 kg/m² and an HR of 2.30 (95% CI 1.26, 4.20) if BMI was <25 kg/m², compared to those with waist circumference less than or equal to median and BMI was <25 kg/m² (Table 3). Waist circumference less than or equal to median and a BMI of ≥25 kg/m² yielded an HR of 1.43 (95% CI 0.87, 2.35).

Additional adjustment for physical activity did not change the results (data not shown). Attributable fractions calculated from the estimated associations suggest that 20.8% of PsA cases in the study population can be attributed to either overweight (8.8%) or obesity (12%).

### Effect of physical activity
Overall, lower levels of physical activity were associated with a slightly higher risk of PsA than the highest physical activity level, although the precision of the estimates was low (Table 2). HRs among moderate, low, and inactive individuals were 1.45 (95% CI 0.98, 2.13), 1.22 (95% CI 0.80, 1.84), and 1.30 (95% CI 0.66, 2.54), respectively. Adjusting for BMI or waist circumference as possible confounders did not change the results.

### Combined effect of physical activity and BMI/waist circumference
Compared to the reference category (BMI <25 kg/m² and high physical activity level), a BMI of ≥25 kg/m² and physical activity at any lower level was associated with a 2-fold increased risk (HR 2.06 [95% CI 1.18, 3.58]), whereas those with a BMI of ≥25 kg/m² and high physical activity level had an HR of 1.53 (95% CI 0.80, 2.91) (Table 4). A BMI of <25 kg/m² and low physical activity level resulted in an HR of 1.27 (95% CI 0.70, 2.30) compared to the reference category. The within-category median value of BMI was similar in the 2 categories of BMI <25 kg/m², as well as in the 2 categories of BMI ≥25 kg/m² (data not shown). There was no evidence of a synergistic effect of overweight/obesity and low physical activity, with a RERI of 0.26 (95% CI –0.65, 1.17). Furthermore, no evidence of interaction was found on a multiplicative scale (P = 0.71).

### Table 3. The combined effect of body mass index (BMI) and waist circumference (WC) on risk of incident psoriatic arthritis (PsA)*

|                 | Normal weight, BMI 18.5–24.9 kg/m² | Overweight/obese, BMI ≥25 kg/m² |
|-----------------|-----------------------------------|---------------------------------|
|                 | Person-years | Cases | Rate† | HR (95% CI)‡ | Person-years | Cases | Rate† | HR (95% CI)‡ |
| WC ≤ median§    | 200,273      | 45    | 2.2   | -            | 87,675       | 25    | 2.9   | 1.43 (0.87, 2.35) |
| WC > median§    | 28,667       | 14    | 4.9   | 2.30 (1.26, 4.20) | 245,182      | 97    | 4.0   | 2.13 (1.49, 3.07) |

* 95% CI = 95% confidence interval; HR = hazard ratio.
† Incidence of PsA per 10,000 person-years.
‡ HR adjusted for age, sex, smoking status, and education status.
§ Median: women, 79 cm; men, 90 cm.

### Table 4. The combined effect of body mass index (BMI) and level of physical activity (PA) on risk of incident psoriatic arthritis (PsA)*

|                 | Normal weight, BMI 18.5–24.9 kg/m² | Overweight/obese, BMI ≥25 kg/m² |
|-----------------|-----------------------------------|---------------------------------|
|                 | Person-years | No. of cases | Rate† | HR (95% CI)‡ | Person-years | No. of cases | Rate† | HR (95% CI)‡ |
| PA high§        | 71,771       | 15           | 2.1   | 1.00 (Ref.)   | 82,961       | 25           | 3.0   | 1.53 (0.80, 2.91) |
| PA low¶         | 148,270      | 42           | 2.8   | 1.27 (0.70, 2.30) | 230,097      | 90           | 3.9   | 2.06 (1.18, 3.58) |

* 95% CI = 95% confidence interval; HR = hazard ratio; Ref. = reference.
† Incidence of PsA per 10,000 person-years.
‡ HR adjusted for age, sex, smoking status, and education status.
§ High PA level.
¶ PA at moderate/low level or inactivity.
Individuals with a high waist circumference (WHO cutoffs: ≥81 cm in women, ≥95 cm in men) and low physical activity had a >2-fold higher risk of developing PsA (HR 2.22 [95% CI 1.37, 3.58]), whereas a high waist circumference and high physical activity level were associated with an HR of 1.84 (95% CI 0.97, 3.47) (Table 5), both compared to the reference category of low waist circumference and high physical activity. The within-category median value of waist circumference was similar in the 2 categories of low waist circumference, as well as in the 2 categories of high waist circumference (data not shown). The RERI estimate for these associations was 0.00 (95% CI = -1.17, 1.17), indicating no synergistic effect above additivity for high waist circumference and low physical activity. Similarly, there was no evidence of interaction on a multiplicative scale (P = 0.85). Sensitivity analyses excluding those with new onset of PsA within the first 3 years after inclusion did not change the above associations (data not shown).

**Table 5.** The combined effect of World Health Organization categories of waist circumference and level of physical activity (PA) on risk of incident psoriatic arthritis (PsA)*

| Normal waist circumference† | High waist circumference‡ |
|-----------------------------|--------------------------|
| Person-years | No. of cases | Rate‡ | HR (95% CI)¶ | Person-years | No. of cases | Rate‡ | HR (95% CI)¶ |
| PA high# | 113,518 | 24 | 2.1 | 1.00 (Ref.) | 41,026 | 16 | 3.9 | 1.84 (0.97, 3.47) |
| PA low** | 222,761 | 68 | 3.1 | 1.38 (0.86, 2.21) | 155,144 | 66 | 4.3 | 2.22 (1.37, 3.58) |

* 95% CI = 95% confidence interval; HR = hazard ratio; Ref. = reference.
† Normal waist circumference: <81 cm for women, <95 cm for men.
‡ High waist circumference: ≥81 cm for women, ≥95 cm for men.
§ Incidence of PsA per 10,000 person-years.
¶ HR adjusted for age, sex, smoking status, and education status.
** PA at moderate/low level or inactivity.

**DISCUSSION**

In this population-based longitudinal study, adiposity, and in particular central obesity, was associated with increased risk of PsA. Individuals reporting low levels of physical activity had a somewhat higher risk of PsA than the most physically active. Although there was no clear evidence of a synergistic effect of physical activity and adiposity on PsA risk, the results suggest that the adverse effect of adiposity was somewhat lower among the most physically active participants. Our data also indicate an increased risk of PsA associated with weight gain, although the precision of these estimates was low.

To our knowledge, this is the first study showing the effect of leisure-time physical activity on risk of developing PsA. However, the results for BMI are in line with previous studies indicating a higher risk of developing PsA in overweight and obese individuals (12,13,36–38). A recent study suggested that the risk of incident PsA among patients with psoriasis can be modified by weight reduction (39). Approximately one-fifth of cases of incident PsA could be attributed to overweight or obesity if the estimated associations reflect causal relations. It has been indicated that excess body weight has a cumulative effect, as obesity in young age increases the risk of PsA (13). Biomechanical factors have been suggested as contributing factors in the development of PsA, and a high BMI results in greater mechanical stress for musculoskeletal structures (40). In the current study, the positive association between adiposity and risk of PsA was stronger for waist circumference than for BMI. Waist circumference may be a more accurate measure of visceral fat than BMI (41), as the latter is influenced by muscle mass. In addition, measure of waist circumference may be a better indicator of metabolic abnormalities and CVD risk (32). In light of the observed results, it is also conceivable that visceral fat plays an important role in the development of PsA. It has been described how complex interactions between the metabolic systems and cells of the immune system have pivotal roles in the pathogenesis of obesity-associated disease. The number of macrophages in adipose tissue in the obese state are triple those in lean adipose tissue, and adipose tissue–activated macrophages secrete high concentrations of proinflammatory cytokines and play a central role in promoting obesity-associated inflammation (42). The proinflammatory cytokines can trigger the interleukin-23/Th17 pathway that plays a pivotal role in the pathogenesis of PsA (43). There is also evidence that obesity can trigger autoinflammation (42), and PsA is partially considered an autoinflammatory disease (44).

In this study, physical activity at high levels seemed to modify the risk of PsA in overweight/obese individuals. However, individuals of normal weight doing low level of physical activity had a slightly increased risk as well. In addition, there was no evidence of a modifying effect of high physical activity level on the association between waist circumference and PsA risk. Thus, excessive fat seemed to be of greater importance than low levels of physical activity. A recent study on CVD risk reported that obesity combined with inactivity was associated with the highest risk of myocardial infarction (MI); however, physical activity seemed to attenuate but...
not eliminate the risk of MI associated with excess body weight (20). Other studies indicate that high-level physical activity reduces abdominal/visceral fat that could lead to a reduction in low-grade inflammation, regardless of BMI (23,45). This could explain the protective effect of physical activity on the risk of both PsA and CVD.

According to the biomechanical stress theory (26,27), high-level physical activity could potentially contribute to the development of PsA due to the mechanical wear in load-bearing joints and in entheses, similar to the effect of a high body mass. However, in our study, high-level physical activity did not increase the risk of PsA, regardless of BMI.

Psoriasis is a major risk factor for PsA, and overweight/obesity is reported to increase the risk of psoriasis (11). A Mendelian randomization study suggested a causal effect of increased BMI on psoriasis (46). A recent meta-analysis also reported increased risk of psoriasis with higher BMI, waist circumference, and weight gain (47). A study conducted in the same population as that in the current study reported increased risk of psoriasis in individuals with high BMI and waist circumference (48), although the associations were somewhat weaker than those observed for PsA. Our results support previous data suggesting that obesity could be a stronger risk factor for development of PsA than for skin psoriasis alone (36).

Strengths of this study include the large sample and population-based, longitudinal design. Furthermore, the diagnoses of PsA have been validated according to stricter criteria than the CASPAR criteria (3). Also, the level of leisure-time physical activity from the questionnaire in HUNT2 has been validated against measured maximum oxygen uptake, and the term “hard leisure time physical activity” performed well (33). This suggests that our category of high-level physical activity represents vigorous activity. However, it is not possible to calculate metabolic equivalent of task hours from the questionnaire data because no information on type of activity was obtained.

Our study has some limitations. Individuals included in the study had to participate in both HUNT2 and HUNT3, and selection bias could have influenced the results if participation in HUNT3 was dependent on physical activity and adiposity status or PsA risk. However, such bias would most likely underestimate the associations under study.

Furthermore, validation of the diagnosis of PsA was accomplished according to stricter criteria than the CASPAR criteria because all validated cases had to include psoriasis to establish a diagnosis of PsA (3). Approximately 15% of all incident PsA patients develop arthritis and psoriasis simultaneously, or PsA precedes psoriasis (49), and thus a few cases of PsA may not have been identified. However, whether this leads to underestimation or overestimation of the associations under study is not clear, and this possibility would require that adiposity and physical activity be associated with these undetected cases in a different way than with the observed cases. Furthermore, based on the selection criteria for the validation study, it is conceivable that some cases of PsA that occurred among individuals with DM were not detected because they did not receive the psoriasis questionnaire. Since DM could be caused by adiposity and inactivity, this could bias the observed association toward the null.

PsA is believed to have a long preclinical phase, and delay between the onset of joint symptoms and diagnosis of PsA could be on average 5 years (50). The prevalence of pain at baseline was higher among inactive participants compared to those with high-level physical activity, which could indicate reverse causality by undiagnosed PsA. However, sensitivity analyses excluding the cases with disease onset within the first 3 years did not change the association of obesity and physical activity with risk of PsA. Last, because there were only a few individuals and cases of PsA in some of the categories, particularly when examining combined effects, the precision of the estimated associations for these categories was low.

In conclusion, the results from this population-based, longitudinal study indicate a positive association of adiposity, and in particular central obesity, with the risk of incident PsA. Although there was no clear modifying effect of physical activity on adiposity, individuals performing high-level physical activity had a reduced risk of PsA, regardless of BMI. Thus, our study adds to the growing evidence that the risk of PsA is modifiable and highlights the importance of preventive work against obesity, as well as the importance of encouraging individuals to engage in physical activity to reduce the incidence of PsA.

ACKNOWLEDGMENTS

The authors thank the clinicians and other employees at Nord-Trøndelag Hospital Trust for contributing to the data collection for this research project.

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. Thomsen 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. Thomsen, Nilsen, Hoff.

Acquisition of data. Thomsen, Nilsen, Hoff.

Analysis and interpretation of data. Thomsen, Nilsen, Haugeberg, Gulati, Kavanaugh, Hoff.

REFERENCES

1. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 2005;53:573.

2. Tam LS, Leung YY, Li EK. Psoriatic arthritis in Asia. Rheumatology (Oxford) 2009;48:1473–7.

3. Hoff M, Gulati AM, Romundstad PR, Kavanaugh A, Haugeberg G. Prevalence and incidence rates of psoriatic arthritis in central Norway: data from the Nord-Trøndelag health study (HUNT). Ann Rheum Dis 2015;74:60–4.

4. Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis 2009;68:1131–5.

5. Jamniktis A, Symmons D, Peters MJ, Saltar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. Ann Rheum Dis 2013;72:211–6.
6. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. Ann Rheum Dis 2016;75:1680–6.

7. Gulati AM, Semb AG, Rollefstad SR, Kavanaugh A, Gulati S, et al. On the HUNT for cardiovascular risk factors and disease in patients with psoriatic arthritis: population-based data from the Nord-Trondelag Health Study. Ann Rheum Dis 2016;75:819–24.

8. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. Arthritis Care Res (Hoboken) 2017;69:67–74.

9. Lupoli R, Pizzicato P, Scalera A, Ambrosino R, Amato M, Peluso R, et al. Impact of body weight on the achievement of minimal disease activity in patients with rheumatic diseases: a systematic review and meta-analysis. Arthritis Res Ther 2016;18:297.

10. Pedreira PG, Pinheiro MM, Szejnfeld VL. Bone mineral density and body composition in postmenopausal women with psoriasis and psoriatic arthritis. Arthritis Res Ther 2011;13:R16.

11. Dainen CI, Sellam J. Obesity and inflammatory arthritis: impact on occurrence, disease characteristics and therapeutic response. RMD Open 2015;1:e000012.

12. Ogdie A, Gelfand JM. Clinical risk factors for the development of psoriatic arthritis among patients with psoriasis: a review of available evidence. Curr Rheumatol Rep 2015;17:64.

13. Russolillo A, Iervolino S, Peluso R, Lupoli R, Di Minno A, Appone N, et al. Obesity and psoriatic arthritis: from pathogenesis to clinical outcome and management. Rheumatology (Oxford) 2013;52:62–7.

14. Gulati AM, Salvesen OS, Thomsen RS, Kavanaugh A, Semb AG, Rollefstad S, et al. Change in cardiovascular risk factors in patients who develop psoriatic arthritis: longitudinal data from the Nord-Trondelag Health Study (HUNT). RMD Open 2018;4:e000630.

15. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol 2010;146:721–6.

16. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391:2273–84.

17. Gerdts S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol 2011;20:81–7.

18. Scortece M, Conde J, Gomez R, Lopez V, Pino J, Gonzalez A, et al. Role of adipokines in atherosclerosis: interferences with cardiovascular complications in rheumatic diseases. Mediators Inflamm 2012;2012:125458.

19. Ouerghi N, Fradji MK, Bezrati I, Khammassi M, Feki M, Kaabachi N, et al. Effects of high-intensity interval training on body composition, aerobic and anaerobic performance and plasma lipids in overweight/ obese and normal-weight young men. Biol Sport 2017;34:385–92.

20. Renninger M, Lochen ML, Ekulund U, Hopstock LA, Jorgensen L, Mathiesen EB, et al. The independent and joint associations of physical activity and body mass index with myocardial infarction: the Tromso Study. Prev Med 2018;116:94–8.

21. Rocha-Rodrigues S, Rodriguez A, Goncalves IO, Moreira A, Maciel E, Santos S, et al. Impact of physical exercise on visceral adipose tissue fatty acid profile and inflammation in response to a high-fat diet regimen. Int J Biochem Cell Biol 2017;87:114–24.

22. Weddell-Neergaard AS, Krogh-Madsen R, Petersen GL, Hansen AM, Pedersen BK, Lund R, et al. Cardiorespiratory fitness and the metabolic syndrome: roles of inflammation and abdominal obesity. PLoS One 2018;13:e0194991.

23. Maillard F, Pereira B, Boisseau N. Effect of high-intensity interval training on total, abdominal and visceral fat mass: a meta-analysis. Sports Med 2018;48:269–88.

24. Helgerud J, Hylヤ1K, Wang E, Karlens T, Berg R, Bjerring M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc 2007;39:665–71.

25. Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, Vatten L, et al. Peak oxygen uptake and cardiovascular risk factors in 4,631 healthy women and men. Med Sci Sports Exerc 2011;43:1465–73.

26. Jacques P, Lambrecht S, Verheugen E, Pauwels E, Kollias G, Armakia, M, et al. Proof of concept: enthesitis and new bone formation in spondyloarthropathies are driven by mechanical strain and stromal cells. Ann Rheum Dis 2014;73:437–45.

27. McGonagle DG, Hellwell P, Veale D. Enthesitis in psoriatic disease. Dermatology 2012;225:100–9.

28. Schett G, Lories RJ, D’Agostino MA, Elemen D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731–41.

29. Krookstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort profile: the HUNT Study, Norway. Int J Epidemiol 2013;42:968–77.

30. Holmen J. The Nord-Trondelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. Norsk Epidemiologi 2003;13:19–32.

31. World Health Organization. Obesity: preventing and managing the global epidemic. 2000. URL: https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/.

32. World Health Organization. Waist circumference and waist-hip ratio. 2008. URL: https://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/.

33. Kurtze N, Rangul V, Hustveit BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trondelag Health Study (HUNT 2). Eur J Epidemiol 2007;22:379–87.

34. Skarpnes ES, Nilsen TI, Sand T, Hagen K, Mork PJ. Do physical activity and body mass index modify the association between chronic musculoskeletal pain and insomnia? Longitudinal data from the HUNT study, Norway. J Sleep Res 2018;27:32–9.

35. Andersson T, Alfredsson L, Kalberg H, Zdankovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575–9.

36. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. Ann Rheum Dis 2012;71:1267–72.

37. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: a population-based study. Ann Rheum Dis 2012;71:1273–7.

38. Scher JJ, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol 2019;15:153–66.

39. Green A, Shaddick G, Charlton R, Snowball J, Nightingale E, Santos S, et al. Modifiable risk factors and the development of psoriatic arthritis among patients with psoriasis. Br J Dermatol 2020;182:714–20.

40. Tonuk SB, Ramadan B, Yorgancioglu ZR. Kinetic factors may trig- er lesion development in the patients with psoriatic arthritis. Int J Rheum Dis 2016;19:1032–4.

41. Lee WS. Body fatness charts based on BMI and waist circumfer- ence. Obesity (Silver Spring) 2016;24:245–9.

42. Kanneganti TD, Dixit VD. Immunological complications of obesity. Nat Immunol 2011;12:707–12.

43. Marioni B, Ceriello A, Massarotti MS, Selmi C. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. Auto Immun Highlights 2014;5:9–19.

44. McGonagle D. Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. J Eur Acad Dermatol Venereol 2009;23 Suppl S:95–13S.

45. Weddell-Neergaard AS, Eriksen L, Gronbaek M, Pedersen BK, Krogh-Madsen R, Tolstrup J. Low fitness is associated with
abdominal adiposity and low-grade inflammation independent of BMI. PLoS One 2018;13:e0190645.

46. Budu-Aggrey A, Brumpton B, Tyrrell J, Watkins S, Modalsli EH, Celis-Morales C, et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. PLoS Med 2019;16:e1002739.

47. Aune D, Snekvik I, Schlesinger S, Norat T, Riboli E, Vatten LJ. Body mass index, abdominal fatness, weight gain and the risk of psoriasis: a systematic review and dose-response meta-analysis of prospective studies. Eur J Epidemiol 2018;33:1163–78.

48. Snekvik I, Smith CH, Nilsen TI, Langan SM, Modalsli EH, Romundstad PR, et al. Obesity, waist circumference, weight change, and risk of incident psoriasis: prospective data from the HUNT Study. J Invest Dermatol 2017;137:2484–90.

49. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:2095–6.

50. Kavanaugh A. Psoriatic arthritis and burden of disease: patient perspectives from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Rheumatol Ther 2016;3:91–102.