INVESTIGATIVE REPORT

High Body Mass Index in Adolescent Girls Precedes Psoriasis Hospitalization

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Psoriasis is associated with being overweight, but the temporal relationship is not known. This historical cohort study tested whether severe psoriasis resulting in hospitalization in adulthood was preceded by excess increase in age-adjusted body mass index, a known risk factor in childhood for being overweight in adulthood. The study cohort was based on the Copenhagen School Health Records Register, birth years 1930 to 1984 (309,152 schoolchildren). Cases were found through the Danish National Patient Register for the period 1977 to 2001. A total of 1074 (0.36%) of the schoolchildren were identified as having psoriasis, with at least one hospital admission. Multivariate analysis demonstrated an association between excess increase in body mass index and psoriasis in females only. Being overweight in adolescence was the main factor behind this observation. The female group showed a significant association between psoriasis and body mass index at ages 12 ($p=0.028$) and 13 years ($p=0.010$). This was not the case for males or for body mass index measured at ages 11 years and below. *Key words: psoriasis BMI; historical cohort; linkage record; epidemiology.*

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Psoriasis is associated with being overweight and with metabolic syndrome. Several cross-sectional studies have demonstrated this association in adulthood, both regarding incidence and clinical severity (1–4). Additionally, it has been noted that patients with psoriasis who are eligible for biological treatment generally were more overweight than the normal population (5, 6). The causal relationship remains elusive, as obesity may be both a cause of and a consequence of having psoriasis. It has been hypothesized previously that psycho-social stigma may lead to secondary obesity in psoriasis patients, but obesity as such is currently regarded as a pro-inflammatory state (7) that may hypothetically be able to alter inflammatory disease according to individual predisposition (8).

Two previous studies have tried to elucidate a possible temporal relationship between being overweight and psoriasis. One study (9) collected information about body mass index (BMI; kg/m²) at onset of psoriasis and compared it with BMI at 18 years of age as recalled by the patients. The conclusion was that psoriasis seemed to precede being overweight, but recall bias was acknowledged in the discussion part of the paper. Another study (10) prospectively examined BMI in nurses from the age of 25 years and retrospectively collected incident cases of self-reported psoriasis during the 14-year follow-up period as well as BMI at the age of 18 years. This study, in contrast, clearly demonstrated that being overweight at the age of 18 years was followed by larger incidences of psoriasis in the follow-up period. A lower BMI was also associated with a reduced incidence of psoriasis. More studies of the temporal relationship between being overweight and psoriasis have recently been requested (11).

Being overweight in childhood is associated with being overweight later in life, but not strongly so. Being overweight in late childhood and weight fluctuations during childhood seem to be the strongest predictors for being overweight in adulthood (12).

The aim of the present study was to test whether severe psoriasis (defined as resulting in hospitalization in adulthood) could be predicted by risk factors for adult obesity, such as weight fluctuations and weight increase during childhood. Traditionally, only moderate to severe cases of psoriasis have been referred to hospital treatment in Denmark. Of these, only the most severe were admitted for inpatient care. Milder cases have been maintained in private practice or as hospital outpatients.

METHODS

School health report data from all schoolchildren attending primary school within the municipality of Copenhagen were available for the study through the Copenhagen School Health Records Register (13). This historical cohort was defined as all children born between 1930 and 1984 with data available on weight and height in the age group 7–13 years. The total number of schoolchildren was 309,152. From these data we calculated the age-specific BMI for each pupil. Deviations from reference BMI z-scores were calculated based on the age- and sex-matched normal BMI distribution in children born in the period 1955 to 1960 (14). Before the start of the study we con-

sidered excess growth of BMI, and fluctuations in BMI during childhood as possible risk indicators for being overweight in adulthood and, according to our hypothesis, consequently also for psoriasis. Growth could not be estimated for schoolchildren with only one height-weight measurement available ($n = 8768$). Through their social security numbers (unique person identifiers) schoolchildren were cross-linked to all patients who were registered within the National Patient Register with a diagnosis of psoriasis (ICD-8 code 696.19 or ICD-10 code L40.0-L40.9) in the period 1977 to 2001. The National Patient Register under the National Board of Health contains all hospital inpatient admissions in Denmark from 1977, and in all cases at least one diagnosis was registered at discharge.

Statistical analysis

Only cases with two or more height-weight measurements at different ages were included in our analysis in order to be able to estimate increase in BMI during childhood. A linear regression model was fitted for each case to estimate the temporal development in z-scores for BMI. The estimated intercept and slope (for each individual), together with gender and year of birth, was then included as a covariate in a multivariate logistic regression model. The effect of the individual slope was tested in order to evaluate whether excess growth in BMI during childhood was associated with moderate to severe psoriasis, defined as inclusion into the National Patient Register with a diagnosis of psoriasis because of an episode of hospitalization. Significance of predictors was based on the likelihood ratio test. All variables were kept in the model if significant at the 5% level.

In accordance with the pre-planned outcome expectations, we also tested a possible effect of variability in BMI on psoriasis. All analyses were repeated on the 80% subset with all 7 possible measurements, and additionally on the same subset after discarding values for the ages 8, 10 and 12 years. This was done in order to test for possible effect of outliers and of data interdependency.

In a subsequent analysis, age- and gender-specific z-scores for BMI was compared for the psoriasis-yes group with the psoriasis-no using two-sided t-tests. All analyses were performed using the statistical software R (15).

RESULTS

The database consisted of 300,384 schoolchildren with at least two height-weight measurements. Approximately 80% of these had all seven measurements possible for ages 7–13 years. From the National Patient Register 1074 (0.36%) of the schoolchildren were identified as psoriasis patients, with slightly more male than female patients (593/152051 vs. 481/148333). The schoolchildren's years of birth followed the national demographic trend, with a comparatively high number born in 1930, peaking in 1945, and declining towards 1980. Patient cases reflected the same pattern (Fig. 1).

A multivariate analysis was designed to test the primary hypothesis that excess gain in BMI during childhood (expressed as the individual slope in temporal BMI development for each person) might be associated with psoriasis. The median BMI z-score at age 10 years was initially chosen as the intercept, because of its position in the middle of our observation range. In this analysis an association was found between excess
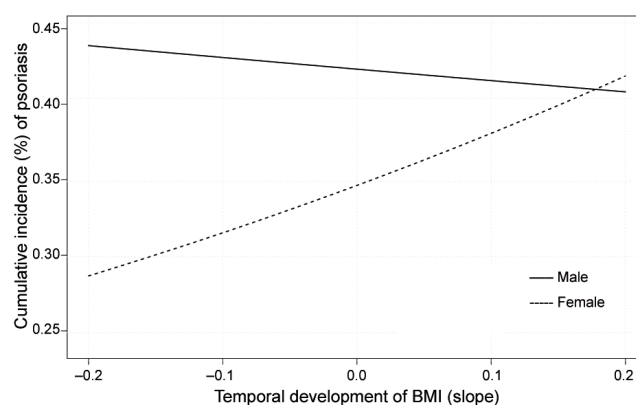

Fig. 1. Cumulative incidence of psoriasis as a function of temporal development of z-scores of body mass index (BMI). A significant association ($p < 0.001$) is found for females, but not for males.

BMI gain during childhood and psoriasis in females, but not in males (Fig. 2).

In order to further validate this result, the model was changed in such a way that the BMI z-score at 13 years of age was used as the intercept instead. This modification of the model, however, annulled the observed effect of excess BMI-gain in females. That observation strongly suggests that the effect observed should be attributed to a higher BMI at age 13 years rather than to the excess BMI-gain as such, and this was confirmed by including the BMI z-score at age 13 in the multivariate analysis. Checking for variability in BMI, as described above, did not alter the results in any way.

In accordance with this, age-specific z-scores for BMI did not show any significant differences between psoriasis patients and non-patients and not in the male subgroup either. The female group, however, showed a significant association between psoriasis and BMI expressed as z-scores at ages 12 and 13 years (Table I).

The most important finding in the study thus appeared to be a marked effect in females on psoriasis from BMI expressed as z-score in early adolescence with an odds ratio for one unit increase in z-score of BMI at age 13 years of 1.49 (95% CI 1.19–1.86). The effect in males was not significant, with an odds ratio for one unit increase in z-score of BMI at age 13 years of 0.87 (95% CI 0.68–1.10). This is illustrated in Fig. 2 by year of birth.

DISCUSSION

This historical cohort study demonstrates an increased risk of admission to hospital for psoriasis in females relating to increased BMI at age 12 and 13 years. The increased risk can be expressed as an increase of 1.49 in odds-ratio for each unit increase in z-score of BMI. A similar effect was, however, not found in males, and the original hypotheses regarding effects from excess
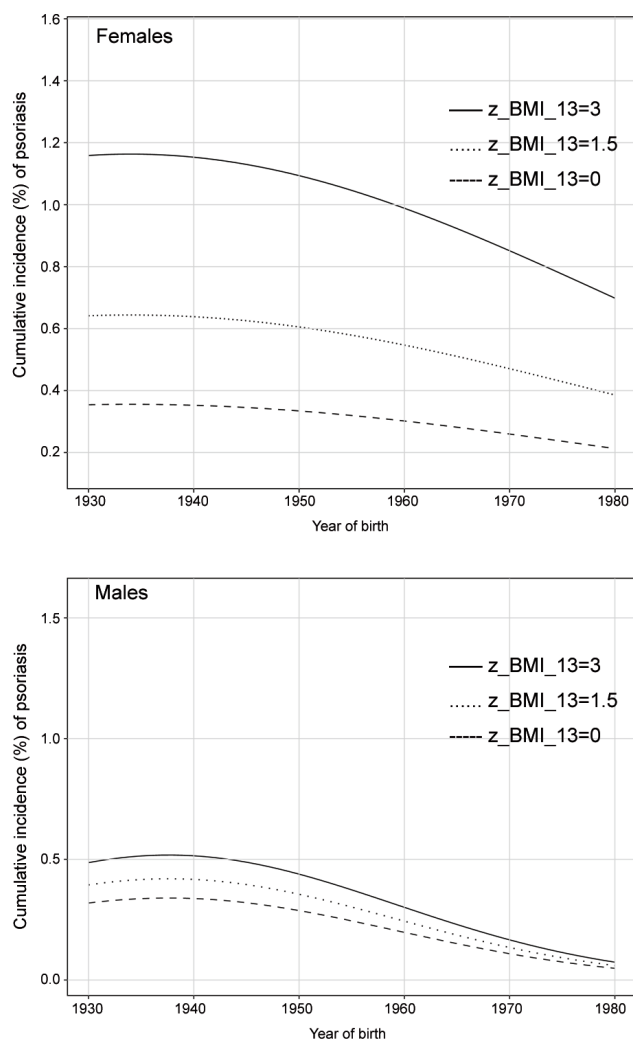
Fig. 2. Cumulative incidence of psoriasis as a function of BMI at age 13 years for female (*top*) and male (*bottom*) by year of birth. The curves denotes psoriasis incidence in persons with average BMI at age 13 (z=0), moderately obese persons (z=1.5) and severly obese persons (z=3). The association is not significant for males, but is significant for females ($p<0.001$).

growth in BMI during childhood or excess BMI in early childhood were not confirmed.

The study benefits from a substantial amount of data, which were collected in a very systematic way for other purposes over a long period of time. The present data on over 300,000 persons exhaustively and systematically examined over several years within a well-defined area strengthens the validity of our findings.

Psoriasis patients have demonstrated a high level of inflammatory mediators, such as tumour necrosis factor (TNF)-α and interleukin (IL)-6, which is also characteristic of patients who are overweight and those with metabolic syndrome (16). Additionally, the satiety hormone leptin has been demonstrated to promote TNF-α and other immunoregulators (17). This supports the hypothesis that being overweight might provoke or worsen psoriasis.

Neither adult psoriasis nor metabolic syndrome generally show sex-differences in prevalence rates, but one previous study has found increased BMI in female same-gender siblings of psoriasis patients (18). A possible explanation might be hidden in the observation that adolescent weight in our study appeared to be more important with respect to psoriasis than early childhood weight development. If any weight gain is important for psoriasis; and if this in some way is connected with onset of puberty (something that would have happened in the great majority of girls but in only a fraction of the boys at ages 12 and 13 years (19)) then an assumed similar association between psoriasis and being overweight in adolescence in males may also exist, but we could not investigate this because of the later onset of puberty.

Some support for our observation may also be found in the sex-ratio in childhood psoriasis. The prevalence of psoriasis is generally thought to be equal between the sexes, but earlier reports have suggested that girls are more often treated for the disease than boys (20, 21). These reports may, on the other hand, also reflect more psychosocial aspects of the disease (22).

Another obvious aspect of a possible peri-menarchal increase in the prevalence of psoriasis is the increased level of sex hormones, in particular oestrogens, which are known to promote keratinocyte proliferation via specific receptor-mediated mechanisms (23–31). This mechanism appears to be significant in the wound-healing process, suggesting that this effect alone may provide a significant stimulus to the development of epidermal hypertrophy characteristic of psoriasis (32, 33).

Sex hormones are also known broadly to influence inflammation (34–37). The increased levels of oestrogen

Table I. *Age- and gender-specific z-scores for body mass index (BMI). The* p-*values are obtained from two-sided* t-*tests comparing the psoriasis-No group with the psoriasis-Yes group for each age and gender combination*

Age, years	Psoriasis in males				Psoriasis in females			
	No	Yes	Difference	*p*-value	No	Yes	Difference	*p*-value
7	0.028	−0.001	0.029	0.457	0.004	0.029	−0.025	0.568
8	0.053	0.046	0.007	0.851	0.043	0.094	−0.051	0.257
9	0.051	0.068	−0.017	0.662	0.050	0.092	−0.042	0.352
10	0.048	0.061	−0.013	0.753	0.055	0.073	−0.018	0.687
11	0.048	0.052	−0.003	0.939	0.051	0.082	−0.031	0.467
12	0.059	0.050	0.009	0.822	0.061	0.161	−0.100	0.028
13	0.076	0.062	0.014	0.729	0.084	0.205	−0.120	0.010

at menarche may influence the Th1 and Th2 immune responses through cytokines and chemokines, including monocyte chemoattractant protein-1 (MCP-1) production (38–41). These changes may stimulate both the cellular activity and TNF-alpha-induced inflammatory response, potentially providing a more direct link to the pathophysiology of psoriasis similar to the situation seen in rheumatoid arthritis, and in direct contrast to, for example, systemic lupus erythematosus (42–45). Looking at the clinical presentation of the disease, it may therefore be suggested that oestrogens aggravate psoriasis (46), while anti-oestrogens may ameliorate it (47, 48).

Great care must, of course, always be taken with the interpretation of findings in any study of this kind. The number of registered psoriasis cases in this study is probably much smaller than the number of actual cases. The reasons for this are that the youngest participants were only followed up from 1984 to 2001, and cases diagnosed prior to the introduction of the National Patient Register in 1977 were not included if they were not admitted after 1977. As the oldest participants were born in 1930, some may have died, emigrated or been in remission from psoriasis before being able to be registered.

Psoriasis was, at that time, one of the most common admission diagnoses in dermatology wards, despite the fact that only a minority of all psoriasis patients was treated as inpatients (49).

Psoriasis inpatients would have significantly more severe clinical manifestations compared with outpatients (49). Furthermore, these patients would all have been referred from dermatology specialists in private practice, and thus qualified as more difficult or severe cases. However, no systematic bias in the coding is likely; and the inaccuracies were not considered to be significant, in view of the fact that only a small fraction of all psoriasis cases would in any case be expected to be subject to treatment in a hospital. The study population therefore invariably contains many false non-cases, and therefore no attempt at evaluating the prevalence, incidence or age of onset has been made. The number of dermatological hospital beds has decreased steadily over time, including the observation period in the present study. In consequence, it has only been possible to admit the most severe cases of skin disease for inpatient care. The present study was, by design, restricted to cases admitted as inpatients, and while these may include some milder cases in the beginning of the observation period in addition to the severe cases mainly admitted later on, a possible bias introduced by this should in all probability detract from the likelihood of noticing the presented association rather than facilitate it. Changes over time in admission thresholds is an important problem, but we have solved this by making all comparisons by BMI levels within birth cohorts, i.e. cohort-specific as it appears clearly from Fig. 1. This should remove most of the possible biases that may derive from the changes over time in admission practice. There may be a bias due to admission rates possibly being dependent on degree of obesity in adults, which is correlated with childhood, but this correlation is not strong, and if there had been such bias mechanism, we would have expected it to operate similarly in the two genders.

Onset of psoriasis can be seen in all age groups, but the most frequent age of onset is between 20 and 30 years (50, 51), and approximately 75% of psoriasis patients are under 40 years of age (50, 52). In addition, the age of onset is regarded as biphasic, having an additional peak incidence between 50 and 60 years of age (50, 53, 54). Cases with familial clustering tend to have an earlier age of onset (55, 56), and one study has observed self-reported age of onset before 16 years in up to one-third of all psoriasis patients, though the finding has not been verified in population-based studies, such as the classic 1948 Faroese study (57). Interestingly, a recent study has confirmed a link between overweight and childhood-onset psoriasis (58). The assumption that being overweight precedes psoriasis is dependent on the presupposition that age of psoriasis onset in our study does not differ systematically from what has been previously reported. As age at registration in this study is, in most cases, different from the patients' true age of onset, our data does not permit us to test for this presupposition, and the apparent decline in incidence by year of birth is probably artificial.

ACKNOWLEDGEMENTS

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