Psoriasis and metabolic and cardiovascular comorbidities in children: A systematic review

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HAL Id: hal-02339753
https://hal.sorbonne-universite.fr/hal-02339753v1

Submitted on 30 Oct 2019

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ABSTRACT

Introduction: Psoriasis is associated with a higher risk of cardiovascular and/or metabolic comorbidity in adults, but discordant data have been reported in children.
Objective: To evaluate the frequency of metabolic and cardiovascular comorbidity in children with psoriasis and to establish whether age at onset of psoriasis correlates with metabolic and cardiovascular comorbidity in adulthood.
Material and methods: We conducted a systematic review on MEDLINE, using PubMed and Ovid. The search was limited to children (< 18 years). The following key words were used: "psoriasis" with "children or childhood or adolescent" and "obesity" or "hypertension" or "diabetes" or "dyslipidemia" or "cardiovascular risk factor" or "myocardial infarction" or "stroke" or "coronaropathy" or "comorbidity". The reference lists of the articles retrieved were checked for additional relevant studies.
Results: A total of 377 potential citations were analyzed. After removing duplicate articles and reviewing eligibility in titles and abstracts, 16 articles remained. The studies analyzed revealed significantly higher risk of overweight and obesity in children with psoriasis, despite the numerous definitions used. Four studies reported higher risk of abdominal obesity in children with psoriasis. Data on hypertension, diabetes, dyslipidemia, metabolic syndrome, and major cardiovascular events suggested there was no higher risk of these comorbidities in children with psoriasis. Two studies suggested that age at onset of psoriasis did not increase the frequency of comorbidity in adulthood.
Conclusion: This systematic review suggests that psoriasis in children is not associated with metabolic and cardiovascular comorbidities, except overweight and obesity, for which higher prevalence is clearly demonstrated in the literature.

1. Introduction

Psoriasis affects 2–3% of the general population in Western countries, and 0.7–1.2% of children [1,2]. Its pathophysiology involves multiple mechanisms, including genetic predisposition, immune mechanisms, and exogenous trigger factors such as stress, drugs, and infection.

Psoriasis in adults is associated with cardiovascular and metabolic comorbidity, particularly diabetes, hypertension, dyslipidemia, and major adverse cardiovascular events (MACEs).

The exact link between these diseases is still debated and not fully understood [3]. Some authors have suggested the concept of "psoriatic march" according to which severe psoriasis may lead to cardiovascular comorbidity, probably through systemic inflammation and insulin resistance, causing endothelial dysfunction, then atherosclerosis, and finally myocardial infarction or stroke [4]. Some studies report that obesity may also induce onset of psoriasis through synthesis of inflammatory adipokines [5–10].

Recently, several studies have reported a link between childhood psoriasis and cardiovascular and metabolic comorbidity, with discordant results. Some authors suggest that all children with psoriasis should be screened for cardiovascular and metabolic comorbidities and propose guidelines [2,11–15].

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We conducted a systematic review to evaluate the frequency of metabolic and cardiovascular comorbidity in children with psoriasis and to determine whether age at onset of the disease correlates with these comorbidities in adulthood.

2. Material and methods

2.1. Search strategy and selection of articles

Bibliographic searches were conducted in December 2016 on MEDLINE, using PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) and Ovid (http://www.ovid.com) as interfaces. No language or date restrictions were applied. The search was limited to children (< 18 years). The search used the following keywords: "psoriasis" in combination with "children" or "childhood or adolescent" and: "obesity" or "hypertension" or "diabetes" or "dyslipidemia" or "cardiovascular risk factor" or "myocardial infarction" or "stroke" or "coronaropathy" or "comorbidity." The reference lists of the articles thus retrieved were checked for additional relevant studies. Each article selected was then analyzed on Google Scholar (https://scholar.google.fr/) in search of articles in which it was cited.

The primary inclusion criteria were developed for initial selection of relevant articles, i. e., studies analyzing the relationship between psoriasis and comorbidities. Two of the authors (A. B. and E. M.) screened titles and abstracts to evaluate this initial relevance. If relevance was unclear, studies were included and subsequently reviewed in greater detail. The two authors performed the search independently according to the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in a meta-analysis.

We then selected cohort and cross-sectional studies published as original articles or as letters if sufficient information was available. Answers to editors were also included when they contained information that was useful to complete the results of an original article. Case reports, reviews, commentaries, editorials, and letters to the authors were not considered eligible. All studies had to be independent, to avoid giving double weight, and had to provide sufficient data concerning their results.

Titles, abstracts, and full-text articles were screened by two authors (A.B. and E.M.), who extracted data using a structured form.

2.2. Data extraction

A data extraction form was developed to collect information:

- general data: year of publication, study design, main focus of study, location, mean age of study population, and number of children included;
- psoriasis information: definition and type of psoriasis; age at onset; psoriasis arthritis;
- control groups: healthy or not, rules for matching (age, gender, location);
- comorbidity evaluation and definition: for each comorbidity;
- statistical information: statistical methods, adjustment for confounding variables (age, gender, location).

Two reviewers (A.B., E.M) independently extracted data from each article, and the two sets of results were compared for concordance and re-reviewed if necessary. Inconsistencies were reviewed until agreement was reached.

The data are summarized in Table 1. The details of each comorbidity are summarized in other tables.

2.3. Statistics

The original aim of the study was to perform a meta-analysis of the results, but this was made impossible by the many different definitions and outcome measures used in the articles.

3. Results

The search strategy yielded 377 potential articles. After removing duplicates and reviewing eligibility in titles and abstracts, 16 articles remained (Fig. 1) [2,11–14,16–28]: eight retrospective case–control studies, four retrospective national registry studies, one retrospective study based on a questionnaire sent to patients, two cross-sectional studies, and one retrospective cohort study. Four studies were from the United States, two each from Germany, France, and Denmark, one each from the Netherlands, Italy, China, Australia, and Portugal, and one international study (Table 1).

Data on age and gender are detailed in Table 1. Overall, 11,787 psoriasis patients (7660 children, 4127 adults) were analyzed. Thirteen studies provided sex ratios: among the 2187 children with gender information, 1119 (51.2%) were male and 1068 (48.8%) female; and among the 4127 adults, 2169 (52.6%) were male, and 1958 (47.4%) female.

Psoriasis was diagnosed by a dermatologist in 12 studies (75.0%), and declared by the patients in one (6.2%). In the other three studies (18.7%), patients were included from a database using the International Statistical Classification of Diseases and Related Health (ICD, 8th to 10th revision).

The study objectives comprised assessment of the frequency of comorbidities in children with psoriasis in ten studies (62.5%), the impact of childhood onset of psoriasis on comorbidity frequency in adulthood in two (12.5%), the relationship between adiposity and severity of psoriasis in one (6.2%), the temporal association between psoriasis and adiposity in one (6.2%), lipoprotein composition in psoriatic patients in one (6.2%), and prediction of severe psoriasis by risk factors for adult obesity in one (6.2%) (Table 1).

3.1. Overweight and obesity

Thirteen studies provided data on overweight and obesity. Overweight was defined in eight studies, obesity in nine, and abdominal obesity in two. Definitions differed, making the results difficult to analyze on common criteria. The definitions comprised body-mass index (BMI: > 85th or > 95th percentile; $n = 5$), International Obesity Task Force criteria (IOTF: $n = 2$), waist circumference (WC: $n = 3$), waist-to-height ratio (WtHR: $n = 3$), or ICD code ($n = 2$) (Table 2). Two studies compared mean BMI, WC, or WtHR values.

Six studies (studies 1, 5–7, 11, 14) reported a higher risk of overweight in children with psoriasis, six (studies 5–7, 11, 14, 16) a higher risk of obesity, four (studies 7, 11, 14, 15) a higher risk of abdominal obesity, and two (studies 2, 13) a higher risk of obesity using ICD-10 code E66. Two studies (studies 15, 16) reported no difference in overweight, one (study 15) no difference in obesity, and one (study 9) no difference in WC. Six studies (studies 4, 7, 9, 11, 12, 16) reported higher BMI but below the threshold for overweight or obesity and three (studies 11, 12, 16) a higher mean WC without analysis in terms of age or gender.

Two studies (studies 5, 6) reported a stronger association between overweight/obesity and disease severity, three (studies 7, 14, 15) no difference, and one no correlation with severity except in the moderate-to-severe psoriasis group, which showed a higher WtHR.

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Table 1
Studies analyzed.

No.	Study	Type of study	Age (years)	Cases (gender)/controls (gender)	Diagnosis of psoriasis	Aim of study	Comorbidities analyzed
1	Boccardi 2009 Italy [16]	Case–control	< 15	96 (52 M/44 F)/100 (43 M/57 F)	Dermatologists	Frequency of overweight	Overweight and obesity
2	Augustin 2010 Germany [2]	National registry (GEK 2005)	< 20	2549 (NR)/331,758 (NR)	ICD-10 Code (L40[a])	Frequency of comorbidities	Overweight and obesity, dyslipidemia, diabetes, hypertension, MACEs
3	De Jager 2010 Netherlands [17]	Retrospective on questionnaire	Adults	1926 (929 M/997 F)/NA	Patients, members of the Dutch Psoriasis Society	Epidemiology and clinical features of psoriasis of childhood (< 18 years) and adult onset	Link between BMI in adulthood and age at onset of psoriasis
4	Bryld 2010 Denmark [18]	Retrospective on cohort (Copenhagen School Health Records Register)	7–13 at inclusion	1074 (593 M/481 F)/300,384 (152,051 M/148,333 F)	ICD-8 code (696.19) or ICD-10 code (L40.0–L40.9) for hospitalized patients	Whether severe psoriasis could be predicted by risk factors for adult obesity	Overweight and obesity. Link between obesity and hospital admission for psoriasis in adulthood
5	Koebnick 2011 USA [12]	Californian registry (KPSC Children's Health Study)	2– < 20	1350 (NR)/710,949 (NR)	ICD-9 code (696.0, 696.1[a]), confirmed by a dermatologist	Frequency of obesity and cardiovascular risk factors	Overweight and obesity, dyslipidemia
6	Zhu 2012 China [19]	Case–control	<15	332 (174 M/158 F)/146 (70 M/76 F)	Dermatologists	Frequency of overweight and obesity	Overweight and obesity
7	Paller 2012 International [14]	Multicenter, cross-sectional	5– < 18	409 (178 M/231 F)/205 (96 M/109 F)	Dermatologists	Relationship between adiposity and severity of psoriasis	Overweight and obesity, hypertension, MACEs
8	Mahé 2013 France [20]	Multicenter, cross-sectional	Adults	2201 (1240 M/961 F)/NA	Dermatologists	Relationship between age at onset of psoriasis and comorbidities during adulthood	Frequency of obesity, dyslipidemia, hypertension, diabetes and MACEs in adulthood according to age at onset of psoriasis
9	Goldminz 2013 USA [21–23]	Case–control	9– < 18	20 (5 M/15 F)/20 (5 M/15 F)	Dermatologists	Frequency of metabolic syndrome	Overweight and obesity, dyslipidemia, diabetes, hypertension, metabolic syndrome
10	Becker 2014 USA [24]	Retrospective	4–17	27 (13 M/14F)/NA	Dermatologists	Temporal association of pediatric psoriasis and increased adiposity	Chronologic link between overweight/obesity and psoriasis onset
11	Torres 2014, Portugal [25]	Case–control	5– < 16	20 (7 M/13 F)/27 (9 M/18 F)	Dermatologists	Frequency of comorbidities	Overweight and obesity, dyslipidemia, diabetes, hypertension, metabolic syndrome
12	Jensen 2014 Denmark [13]	Case–control	10– < 18	30 (16 M/14 F)/30 (16 M/14 F)	Dermatologists	Cardiovascular risk factors	Overweight and obesity, dyslipidemia, diabetes, hypertension, MACEs
13	Augustin 2015 Germany [11]	National registry (GEK 2009)	<18	1313 (NR)/291,868 (NR)	ICD-10 code (L40[a])	Analysis of comorbidity reporting bias and confirmation of frequency of comorbidities	Overweight and obesity, dyslipidemia, diabetes, hypertension, MACEs
14	Mahé 2015 France [26]	Case–control, multicenter	2– < 18	261 (126 M/135 F)/261 (126 M/135 F)	Dermatologists	Frequency of overweight and obesity	Overweight and obesity, dyslipidemia, diabetes, hypertension
15	Lee 2016 Australia [27]	Case–control, multicenter	5– < 16	135 (62 M/73 F)/73 (36 M/37 F)	Dermatologists	Analysis of central adiposity, metabolic syndrome and BMI	Overweight and obesity, hypertension, metabolic syndrome
16	Tom 2016 USA [28]	Case–control	0– < 18	44 (19 M/25 F)/44 (19 M/25 F)	Dermatologists	Lipoprotein composition and function	Overweight and obesity, dyslipidemia, diabetes, hypertension

F, female; M, male; NA, not applicable; NR, not reported; ICD-8, ICD-9, ICD-10, International Statistical Classification of Diseases and Related Health Problems, 8th, 9th, 10th revision.
[a] Including: Cases: Brazil, Canada, Chile, United States, Italy, Netherlands, Turkey, United Kingdom and Malaysia; Controls: United States, Netherlands, Italy and Malaysia.
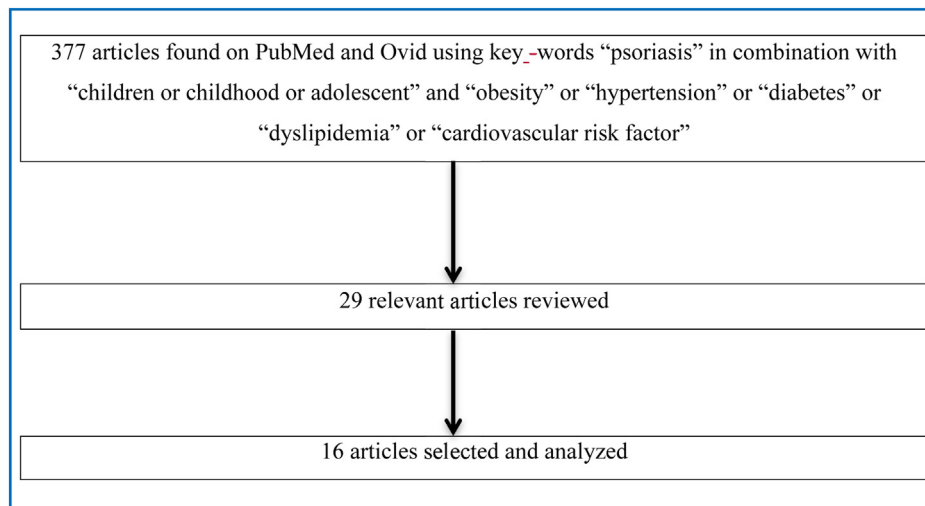
Fig. 1. Flow chart.

3.2. Dyslipidemia

Eight studies reported data on dyslipidemia. Dyslipidemia was defined in one study as LDL and/or TG > 95th age- and gender-specific percentile and/or HDL < 5th percentile, and was reported as an ICD-10 code in two other studies. The other five studies compared levels of total cholesterol, LDL, HDL, TG, or other lipid proteins such as VLDL or apolipoproteins between psoriasis and control groups (Table 3).

Two studies (studies 2, 13) reported higher prevalence of dyslipidemia in the psoriasis group using the ICD-10 code and two (studies 11, 14) no difference. Three studies (studies 9, 12, 16) reported no difference in total or LDL-cholesterol, five (studies 5, 9, 11, 12, 16) no difference in HDL-cholesterol, four (studies 9, 11, 12, 16) no difference in triglyceridemia, two (studies 12, 16) no difference in other lipid proteins such as VLDL or apolipoproteins, except for two specific proteins: apolipoprotein B and large-HDL (study 16). One study (study 5) reported a higher level of total cholesterol and LDL in the psoriasis group without reaching the threshold for hyperlipidemia.

3.3. Diabetes/insulin resistance

Data on diabetes were reported in seven studies. Diabetes was defined in one study as fasting blood glucose > 126 mg/dL or $HbA_{1c} \geq 6.5\%$; homeostatic model assessment (HOMA) for insulin resistance > 3.16 in four studies, and ICD-10 code in two studies. There was no definition of diabetes in the other five studies (Table 4).

One study (study 2) reported a significantly higher risk of diabetes in children with psoriasis. Two other studies (studies 9, 12) reported higher plasma glucose but without reaching the threshold for diabetes, and one (study 16) reported higher log-transformed HOMA. The other six studies (studies 9, 12–14, 16) reported no difference in diabetes according to psoriasis status.

3.4. Hypertension

Data on hypertension were reported in nine studies. Hypertension was defined in four studies as: arterial blood pressure > 90th percentile in one, diastolic and/or systolic blood pressure > 95th percentile in one, and by ICD-10 code in two studies (Table 5).

Two studies (studies 2, 13) reported significantly higher prevalence of hypertension in children with psoriasis, using the ICD-10 code, two (studies 8, 12) reported higher systolic blood pressure without reaching the threshold for hypertension, two (studies 8, 12) higher diastolic blood pressure without reaching the threshold for hypertension, two (studies 11, 14) no difference in diastolic/systolic/blood pressure, and four (studies 8, 9, 15, 16) no difference in systolic or diastolic blood pressure.

3.5. Metabolic syndrome

Data on metabolic syndrome were reported in three studies. Definitions are detailed in Table 6. Only one study (study 9) showed higher prevalence of metabolic syndrome in children with psoriasis; the two other (studies 11, 15) reported no difference. One (study 15) reported no correlation with severity of psoriasis.

3.6. Cardiovascular risks, dysfunction, or MACEs

Four studies reported data on cardiovascular risks, dysfunction, or adverse events (stroke, ischemic heart disease, or reactive hyperemia index (RHI)). The cumulative prevalence of ischemic heart disease was defined by ICD-10 code in two studies, cardiovascular risk by WtRH > 0.49 in one (study 7), and cardiovascular dysfunction by RHI in one (measure of endothelial function) (study 12) (Table 7).

Two studies (studies 2, 13) reported no difference in prevalence of ischemic heart disease. Interestingly, ischemic heart disease was reported in 0.75% of cases in one study (study 2) and in 0.08% in another (study 13), although these studies used the same methodology in the same population. One study (study 7) reported higher WtHR in the psoriasis group but without reaching the threshold for intermediate cardiovascular risk. One study (study 12) reported no difference in RHI.

3.7. Chronologic links between childhood psoriasis and comorbidities

Four studies assessed possible chronologic links between childhood psoriasis and onset of comorbidity (studies 3, 4, 8, 10). Two (studies 3, 10) assessed possible correlation between age at onset of psoriasis and BMI in adulthood. One (study 3) reported significantly higher BMI in adulthood in patients with adult compared to childhood onset of psoriasis (26.8 vs. 24.2; $P = 0.015$) on univariate analysis (no multivariate analysis performed). One (study 4) reported that higher BMI at the age of 12–13 years was associated with hospital admission for psoriasis in adulthood. One (study 10) reported that overweight or obesity preceded psoriasis by more than 2 years in 93% of children suffering from psoriasis.

Table 2
Childhood psoriasis, overweight, and obesity.

No.	Studies	Definition of overweight and obesity	Results: psoriasis vs. control
1	Boccardi 2009, Italy [16]	Overweight: current weight/50th percentile weight at age > 110%	Overweight: 42 (48%) vs. 24 (27%). Odds ratio (95% CI): 2.55 (1.31–4.96)
2	Augustin 2010, Germany [2]	ICD-10 Code (E66[a])	8.40% vs. 4.90%. Prevalence (95% CI): 1.70 (1.49–1.93)
4	Bryld 2010, Denmark [18]	NR (comparison of BMI and deviation from BMI z-score for age and gender)	No difference in BMI for males aged 7–13 years or girls aged 7–11 years. Girls, 12 years, BMI z-score: 0.161 vs. 0.061; $P = 0.028$ Girls, 13 y, BMI z-score: 0.205 vs. 0.084; $P = 0.010$
5	Koebnick 2011, USA [12]	Overweight: BMI > 85th and < 95th percentile or BMI ≥ 25 kg/m² and < 30 kg/m² Obesity: BMI > 95th percentile or BMI ≥ 30 kg/m² Extremely obese: BMI × 1.2 ≥ 95th percentile or BMI ≥ 35 kg/m²	Overweight: OR (95% CI): 1.30 (1.14–1.49) Moderate obesity: OR (95% CI): 1.38 (1.18–1.62) Extreme obesity: OR (95% CI): 1.78 (1.48–2.14) Increased association with disease severity[a]
6	Zhu 2011, China [19]	International Obesity Task Force (IOTF) definition	Overweight: 52 (15.7%) vs. 11 (7.5%). OR (95% IC): 2.4 (1.2–4.8); $P < 0.0$ Obesity: 30 (9.0%) vs. 6 (4.1%). OR (95% IC): 2.6 (1.0–6.4); $P < 0.05$. Disease severity was associated with BMI [b]
7	Paller 2012, International [14]	Overweight: BMI ≥ 85th and <95th percentile (CDC curves) or BMI ≥ 25 kg/m² and < 30 kg/m² Obesity ≥ 95th percentile (CDC curves) or BMI ≥ 30 kg/m²	Overweight: 72 (17.6) vs. 27 (13.2%); obese: 83 (20.2%) vs. 15 (7.3%); $P < 0.001$. OR (95% CI): 2.65 (1.70–4.15). No link to severity (mild vs. severe) of psoriasis [c] BMI percentile, mean ± SD: 63.8 ± 31.8 vs. 54.9 ± 29.6; $P < 0.001$. OR (95% CI): 1.42 (0.96–2.10). No link to severity (mild vs. severe) of psoriasis [c] WC: 75th to ≤90th percentile: 64 (16.2%) vs. 38 (18.6%); >90th percentile: 70 (17.7%) vs. 19 (9.3%); $P = 0.049$. No link to severity (mild vs. severe) of psoriasis[c]
9	Goldminz 2013, USA [21–23]	NR (comparisons of BMI and WC)	BMI (kg/m²), mean ± SD: 22.5 ± 5.4 vs. 22.7 ± 5.7; $P = 0.89$ WC (cm), mean ± SD: 81.1 ± 16. vs. 0 77.6 ± 13.2; $P = 0.42$
11	Torres 2014, Portugal [25]	Overweight: BMI > 85th percentile, WC > 75th percentile Obesity > 95th percentile, WC > 90th percentile	Overweight: 7 (35%) vs. 6 (22.2%); obesity: 4 (25%) vs. 1 (3.7%); $P = 0.03$ WC > 75th percentile: 10 (50%) vs. 4 (14.8%); WC > 90th percentile: 4 (25%) vs. 10 (14.8%); $P = 0.015$ BMI (kg/m²), mean ± SD: 21.1 ± 4.0 vs. 19.0 ± 2.9; $P = 0.011$ WC (cm), mean ± SD: 73.5 ± 11.7 vs. 67.9 ± 10.1; $P = 0.028$
12	Jensen 2014, Denmark [13]	NR (comparisons of BMI and WC)	BMI (kg/m²), mean ± SD: 20.3 ± 0.6 vs. 18.7 ± 0.5; $P = 0.036$ WC (cm), mean ± SD: 72.0 ± 1.8 vs. 66.0 ± 1.0; $P = 0.004$
13	Augustin 2015, Germany [11]	ICD-10 Code (E66[a])	7.08% vs. 3.61%. Prevalence rate (95% CI): 1.89 (1.53–2.34)
14	Mahé 2015, France [26]	Overweight: BMI > 90th percentile (French curves) Obesity: BMI > IOTF-30 (International definition) Abdominal obesity: WtHR > 0.5	Overweight: 6 (2.3%) vs. 15 (5.7%); $P = 018$ Overweight with abdominal obesity: 22 (8.4%) vs. 19 (7.3%). $P = 0.009$ Obesity: 26 (10.0%) vs. 8 (3.1%). $P = 0.001$ Frequency higher in females ($P = 0.048$), if overweight in parents ($P < 0.02$). No impact of disease severity[a] or clinical type of psoriasis
15	Lee 2016, Australia [27]	Overweight: BMI > 85th percentile Obesity: BMI > 95th percentile Increased central obesity: WtHR > 0.5	Overweight: 18 (13%) vs. 9 (12%); obese: 5 (4%) vs. 3 (4%); $P = 0.97$ WtHR, mean ± SD: 0.47 vs. 0.46; $P = 0.36$ WtHR >0.5: 39 (29%) vs. 8 (11); $P = 0.002$. OR (95% CI): 3.30 (1.45–7.52) No correlation with severity of psoriasis except for WtHR ratio higher in moderate to severe psoriasis[d]
16	Tom 2016, USA [28]	Overweight: BMI > 85th to ≤ 95th percentile Obesity: BMI > 95th percentile	Overweight: 20% vs. 16% Obesity: 27% vs. 9% BMI (kg/m²), mean ± SD: 23.5 ± 6.1 vs. 21.4 ± 4; $P = 0.03$ WC (cm), mean ± SD: 80.5 ± 17.9 vs. 74.3 ± 12.5; $P = 0.04$ WtHR, mean ± SD: 0.85 ± 0.06 vs. 0.80 ± 0.06; $P < 0.001$

BMI: body mass index (kg/m²); WC: waist circumference; WtHR: waist-to-height ratio; CDC: Centers for Disease Control and Prevention; ICD: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CI: confidence interval; OR: odds ratio; PASI: Psoriasis Area Severity Index; SD: standard deviation.

[a] Severity of psoriasis defined by the use of systemic treatments.

[b] Severity of psoriasis defined by PASI.

[c] Severity of psoriasis definition: mild psoriasis = worst Physician's Global Assessment score 1 or 2, or 3 with body surface area (BSA) ≤ 10%; severe = worst Physician's Global Assessment score 4 or 5, or 3 with BSA > 10%.

[d] Children were graded, according to the worst severity recorded in the patient files, as having mild psoriasis if BSA involvement was < 10; static Physician's Global Assessment (sPGA) score, ≤ 2; and Psoriasis Activity Severity Index (PASI) < 10; and moderate to severe psoriasis if BSA ≥ 10; SPGA > 2; or PASI ≥ 10.

Finally, one study (study 8) analyzed the frequency of obesity, dyslipidemia, hypertension, diabetes, and MACEs in adulthood according to age of onset of psoriasis and found no significant difference between the age of onset and the frequency of comorbidities in adulthood (Table 8).

4. Discussion

Over the past 10 years, there has been an increase in the number of studies confirming links between psoriasis and metabolic and cardiovascular comorbidities in adults. In children, the studies we analyzed revealed significantly higher risk of overweight and obesity in children with psoriasis, despite the variety of definitions used for overweight and obesity. A correlation was found between overweight and/or obesity and severity of psoriasis in only two studies but was not confirmed by three others. These results are,

however, difficult to compare, due to the differences in definitions of overweight and obesity. Since 2000, definitions of overweight and obesity in children have been consensually based on international data and linked to the widely accepted adult cut-off points of BMI 25 kg/m² and 30 kg/m² [29], although other definitions also exist. This link could be explained by induction of psoriasis by cytokines coming from adipose tissue.

Eight studies reported data on dyslipidemia. The two studies reporting significantly higher prevalence of dyslipidemia in psoriasis used an ICD-10 code definition. None of the other studies in which lipoproteins were measured reported higher risk of dyslipidemia in children with psoriasis. It should be noted that there is no consensual definition of dyslipidemia in children. The American Heart Association [30] and the American Academy of Pediatrics [31] set a cut-off point for LDL-cholesterol (LDLc) at 1.90 g/L in children with no comorbidities, but with slight differences according to age and type of comorbidity. The

Table 3
Childhood psoriasis and dyslipidemia.

No.	Studies	Definition of dyslipidemia	Results: psoriasis vs. control
2	Augustin 2010, Germany [2]	ICD-10 code (E78[a])	2.12% vs. 0.99%. Prevalence rate (95% CI): 2.15 (1.65–2.80)
5	Koebnick 2011, USA [12]	NR (measurement of LDL, HDL, total cholesterol, and TG)	Among overweight and obese patients: Total cholesterol, mg/dL, mean ± SD: 169.6 ± 4.2 vs. 163.9 ± 3.6; $P = 0.021$ HDL-cholesterol, mg/dL, mean ± SD: 45.3 ± 2.9 vs. 45.4 ± 2.8; $P = 0.937$ LDL-cholesterol, mg/dL, mean ± SD: 103.9 ± 4.1 vs. 98.4 ± 3.5; $P = 0.007$ TG, mg/dL, mean ± SD: 114.4 ± 16.4 vs. 100.6 ± 13.8; $P = 0.015$
9	Goldminz 2013, USA [21–23]	NR (measurement of LDL, HDL, total cholesterol, and TG)	Total cholesterol, mg/dl, mean ± SD: 152.9 ± 36.09 vs. 156.3 ± 23; $P = 0.75$ HDL cholesterol, mg/dL, mean ± SD: 44.3 ± 9.5 vs. 49.7 ± 8.9; $P = 0.16$ LDL cholesterol, mg/dL, mean ± SD: 95.1 ± 32.5 vs. 95.1 ± 19.2; $P > 0.99$ TG, mg/dL, mean ± SD: 68.0 ± 26.2 vs. 58.4 ± 17.4; $P = 0.24$
11	Torres 2014, Portugal [25]	LDL and/or TG > 95th age-, sex-specific percentile and/or HDL < 5th percentile	HDL-C <50 mg/dL. 8 (40%) vs. 10 (37%); $P = 1$ TG ≥100 mg/dL: 2 (10%) vs. 2 (7.4%); $P = 1$ Dyslipidemia: 3 (15%) vs. 2 (7.4%); $P = 0.68$
12	Jensen 2014, Denmark [13]	NR (measurement of LDL, HDL, VLDL, total cholesterol, and TG)	Total cholesterol, mmol/L, mean ± SD: 3.8 ± 0.1 vs. 3.9 ± 1.4; $P = 0.702$ HDL cholesterol, mmol/L, mean ± SD: 1.25 ± 0.05 vs. 1.29 ± 0.06; $P = 0.519$ LDL cholesterol, mmol/L, mean ± SD: 2.1 ± 0.1 vs. 2.2 ± 0.1; $P = 0.67$ VLDL cholesterol, mmol/L, median (IQR): 0.4 (0.2–0.6) vs. 0.4 (0.3–0.4); $P = 0.913$ TG, mmol/L, mean ± SD 0.96 ± 0.09 vs. 0.95 ± 0.10; $P = 0.876$
13	Augustin 2015, Germany [11]	ICD-10 code (E78[a])	1.14% vs. 0.64%. Prevalence (95% CI): 1.79 (1.08–2.99)
14	Mahé 2015, France [26]	NR (diagnosis declared by dermatologist)	7 (3.0%) vs. 2 (0.8%); $P = 0.08$
16	Tom 2016, USA [28]	NR (measurement of LDL, HDL, VLDL, total cholesterol, Apo, and TG)	No differences for: total cholesterol, LDL-cholesterol, HDL-cholesterol, TG, Apo A, VLDL particles, LDL particles Apo B, mg/dL, mean ± SD: 72.4 ± 18.1 vs. 64.6 ± 16.2; $P = 0.02$ Large HDL-particle, μmol/L, mean ± SD: 5.3 ± 2.9 vs. 6.7 ± 2.5; $P < 0.01$ Cholesterol efflux capacity, mean ± SD: 0.90 ± 015 vs. 0.95 ± 0.12. $P = 0.002$

NR: not reported; ICD: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CI: confidence interval; SD: standard deviation; IQR: interquartile range; TG: triglycerides; Apo: apolipoprotein.

definition may vary according to children's origin. For example, two French studies reported a 95th percentile for LDLc of 1.64 g/L and 1.49 g/L in males and 1.74 g/L and 1.55 g/L in females [32–34], which is lower than the American cut-off. The absence of a consensual definition casts doubt on the relevance of the ICD-10 code used in the two studies reporting a significant difference, and a higher risk of dyslipidemia in children with psoriasis cannot be said to have been demonstrated.

Seven studies reported data on diabetes and insulin resistance, only one finding a significantly higher risk of diabetes in psoriasis. This study reported diabetes using an ICD-10 code, and we tend to believe the findings could be irrelevant, given that the ICD-10 code and registry studies can show several biases. Moreover, the same type of study conducted 5 years later found no significant difference between psoriasis patients and controls. Other studies reported higher plasma glucose levels, but without reaching the threshold for diabetes, and one reported a higher log-transformed HOMA, suggesting a link between insulin resistance and psoriasis. An increased inflammatory state is indeed associated with both insulin resistance and psoriasis and could explain this link.

Nine studies reported data on hypertension, only two finding a significantly higher risk of hypertension in children with psoriasis. These studies also used an ICD-10 code to define hypertension, which may have led to biases. Two other studies reported higher systolic or diastolic blood pressure in children with psoriasis, but without reaching the threshold for hypertension, and with differences that were subclinical (4 or 6 mmHg). Moreover, the definition of hypertension in children is not consensual, although usually taken as > 95th percentile for gender, age, and height [35]. Therefore, a higher risk of hypertension in children with psoriasis has not been demonstrated.

Very few studies reported data on metabolic syndrome and MACEs. In adults, six different definitions of metabolic syndrome were published between 1988 and 2005 [36–41]. Metabolic syndrome is related to a higher risk of adverse cardiovascular

events in adults, but its definition in children is still debated. Mimoun et al. [42] suggested that the value of metabolic syndrome as a predictor of future cardiovascular events was unclear in children and needed further prospective studies. We therefore do not believe that metabolic syndrome should be analyzed as a criterion in childhood psoriasis until it is clearly defined in children. In a recent meta-analysis, Pietrzak et al. [43] assessed metabolic disorder in children with psoriasis, analyzing data from seven studies with a total of 965 children. Three of the seven studies assessed prevalence of metabolic syndrome, and in all three the rate of metabolic syndrome was significantly higher in case of psoriasis. The authors also showed a significantly higher concentration of fasting glucose and a lower level of HDL-cholesterol in patients with psoriasis but without reaching the abnormal cut-off.

None of the four studies reporting data on MACEs, cardiovascular risk, or dysfunction showed a difference between children with psoriasis and controls. Surprisingly, Augustin et al. [2] reported a 0.75% cumulative prevalence of ischemic heart disease in children with psoriasis, which does not correspond to real life: the rate seems very high and is even higher than in another study they published 5 years later using the same methodology, suggesting a probable bias in the ICD-10 code.

One of the four studies analyzing a potential chronologic link between childhood psoriasis and comorbidities reported a correlation with BMI in adulthood, but with a slightly significantly higher mean BMI in patients with adult rather than childhood onset of psoriasis. Becker et al. [24] reported a potential link between overweight/obesity and child psoriasis, overweight or obesity preceding psoriasis by more than 2 years in 93% of children with psoriasis. Bryld et al. [18] also reported a link between obesity and psoriasis, showing that high BMI in 12- to 13-year-old girls was associated with more severe psoriasis leading to hospital admission. However, the only group showing a significant difference in their study was 12- to 13-year-old girls, without

Table 4
Childhood psoriasis and diabetes/insulin resistance.

No.	Studies	Definition of diabetes	Results: psoriasis vs. control
2	Augustin 2010, Germany [2]	ICD-10 Code (E11, E13, E14)	0.86% vs. 0.43%. Prevalence (95% CI): 2.01 (1.32–3.04)
9	Goldminz 2013, USA [21–23]	NR (comparison of fasting blood glucose)	Glucose, g/dL, mean $\pm$ SD: 91.1 $\pm$ 7.4 vs. 82.9 $\pm$ 10.3; $P=0.01$
11	Torres 2014, Portugal [25]	Fasting blood glucose > 126 mg/dL or HbA1c $\geq$ 6.5% Insulin resistance: HOMA > 3.16	Diabetes: 0 vs. 0 Insulin resistance: 1 (5%) vs. 3 (11.1%); $P=0.6$
12	Jensen 2014, Denmark [13]	NR (comparison of fasting blood glucose, and glycated hemoglobin)	Glucose, mmol/L, mean $\pm$ SD: 5.3 $\pm$ 0.2 vs. 4.9 $\pm$ 0.1 0; $P=0.043$ Glycated hemoglobin, %, mean $\pm$ SD 5.25 $\pm$ 0.11 vs. 5.19 $\pm$ 0.04; $P=0.596$
13	Augustin 2015, Germany [11]	ICD-10 Code (E11, E13, E14)	0.61% vs. 0.31%. Prevalence (95% CI): 1.97 (0.98–3.96)
14	Mahé 2015, France [26]	NR (diagnosis by dermatologist)	0 vs. 0
16	Tom 2016, USA [28]	NR (comparison of insulin resistance: HOMA-IR)	Glucose, mg/dL, mean $\pm$ SD: 79.5 $\pm$ 7.8 vs. 80.1 $\pm$ 8.1; $P=0.63$ HOMA-IR 2.41 $\pm$ 1.83 vs. 1.99 $\pm$ 1.38; $P=0.11$ Log-transformed HOMA-IR 0.65 $\pm$ 0.68 vs. 0.41 $\pm$ 0.88; $P=0.07$

NR; not reported; ICD; International Statistical Classification of Diseases and Related Health Problems 10th Revision; CI; confidence interval; HOMA; the Homeostatic Model Assessment for Insulin Resistance; SD; standard deviation.

Table 5
Childhood psoriasis and hypertension.

No.	Studies	Definition of hypertension	Results: psoriasis vs. control
2	Augustin 2010, Germany [2]	ICD-10 code (I10* … I13*)	1.5% vs. 0.83%. Prevalence (95% CI): 1.89 (1.47–2.67)
7	Paller 2012, International [14]	NR (comparison of BP)	International evaluation: Systolic BP (mmHg), mean $\pm$ SD: 110 $\pm$ 12 vs. 114 $\pm$ 11; $P=0.008$ Diastolic BP (mmHg), mean $\pm$ SD: 67 $\pm$ 8 vs. 66 $\pm$ 9; $P=0.80$ In US participants: Systolic BP (mmHg), mean $\pm$ SD: 110 $\pm$ 12 vs. 110 $\pm$ 12; $P=0.74$ Diastolic BP (mmHg), mean $\pm$ SD: 67 $\pm$ 8 vs. 64 $\pm$ 10; $P=0.46$. Diastolic BP higher in mild psoriasis ($P=0.049$)
9	Goldminz 2013, USA [21–23]	Arterial blood pressure > 90th percentile	Systolic BP (mmHg), mean $\pm$ SD: 111.7 $\pm$ 8.5 vs. 110.2 $\pm$ 9.5; $P=0.64$ Diastolic BP (mmHg), mean $\pm$ SD: 70.9 $\pm$ 8.5 vs. 69.8 $\pm$ 5.6; $P=0.65$
11	Torres 2014, Portugal [25]	Systolic and/or diastolic BP $\geq$ the 95th age-, sex-, and height-specific percentile	Hypertension: 2 (10 3%) vs. 1 (3.7%); $P=0.567$ Systolic BP/diastolic BP >90th percentile: 6 (30%) vs. 1 (3.7%); $P=0.032$
12	Jensen 2014, Denmark [13]	NR (comparison of systolic and diastolic BP)	Systolic BP (mmHg), mean $\pm$ SD: 105 $\pm$ 2 vs. 99 $\pm$ 2; $P=0.023$ Diastolic BP (mmHg), mean $\pm$ SD: 66 $\pm$ 2 vs. 64 $\pm$ 1 2; $P=0.354$
13	Augustin 2015, Germany [11]	ICD-10 code (I10* … I13*)	0.91% vs. 0.44%. Prevalence (95% CI): 2.09 (1.18–3.69)
14	Mahé 2015, France [26]	NR (diagnosis by dermatologist)	2 (0.8%) vs. 0 (0%); $p=0.15$
15	Lee 2016, Australia [27]	NR (comparison of BP)	Systolic BP (mmHg), mean $\pm$ SD: 104.6 $\pm$ 10.1 vs. 102.8 $\pm$ 12.3; $P=0.26$ Diastolic BP (mmHg), mean $\pm$ SD: 66.5 $\pm$ 5.8 vs. 66.7 $\pm$ 7.1; $P=0.80$
16	Tom 2016, USA [28]	NR (comparison of BP)	Systolic BP (mmHg), mean $\pm$ SD: 116 $\pm$ 11 vs. 116 $\pm$ 15; $P=0.57$ Diastolic BP (mmHg), mean $\pm$ SD: 63 $\pm$ 9 vs. 66 $\pm$ 9; $P=0.1$

NR: not reported; ICD: International Statistical Classification of Diseases and Related Health Problems 10th Revision; BP: blood pressure; SD: standard deviation; CI: confidence interval.

Table 6
Childhood psoriasis and metabolic syndrome.

No.	Studies	Definition of metabolic syndrome	Results (psoriasis vs. control)
9	Goldminz 2013, USA [21–32]	$\geq$ 3 of the following: waist circumference $\geq$ 75th percentile TG $\geq$ 100 mg/dL HDL-cholesterol <50 mg/dL (or < 45 mg/dL for boys aged 15–17 years) fasting blood glucose $\geq$ 110 mg/dL systolic or diastolic blood pressure $\geq$ 90th percentile	6 (30%) vs. 1 (5%); $P<0.05$
11	Torres 2014, Portugal [25]	$\geq$ 3 of the following: waist circumference $\geq$ 75th percentile TG $\geq$ 100 mg/dL HDL-cholesterol < 50 mg/dL fasting blood glucose $\geq$ 110 mg/dL systolic or diastolic blood pressure $\geq$ 90th percentile	4 (25%) vs. 1 (3.7%); $P=0.07$
15	Lee 2016, Australia [27]	Increased central adiposity ($\geq$ 90th percentile, adjusted for sex and race), and $\geq$ 2 of the following (only if age $\geq$ 10 years): TG $\geq$ 1.7 mmol/L HDL-cholesterol < 1.03 in boys or 1.29 in girls or undergoing medical therapy for low HDL-cholesterol systolic BP $\geq$ 130 mmHg or diastolic BP $\geq$ 85 mmHg or undergoing treatment for previously diagnosed hypertension fasting glucose level $\geq$ 5.6 mmol or previously diagnosed type-2 diabetes	4/53 (8%) vs. 0/29 (0%); $P=0.29$ No correlation with disease severity

TG: triglycerides; BP: blood pressure.

Table 7
Childhood psoriasis and cardiovascular risk, dysfunction, or MACEs.

No.	Studies	Events evaluated	Results (psoriasis vs. control)
2	Augustin 2010, Germany [2]	ICD-10 code (ischemic heart disease, I20[a] … I25[a])	0.75% vs. 0.49%. Prevalence rate (95% CI): 1.52 (0.97–2.38)
7	Paller 2012, International [14]	High cardiovascular risk: WtHR ≥ 0.539 Intermediate cardiovascular risk: WtHR ≥ 0.490	WtHR, mean ± SD: 0.48 ± 0.08 vs. 0.46 ± 0.05; $P = 0.002$. OR (95% CI): 1.45 (0.96–2.19). No link to severity of psoriasis (mild vs. severe)[a]
12	Jensen 2014, Denmark [13]	RHI (measurement of endothelial function)	RHI, median (IQR): 2.03 (1.53–2.19) vs. 1.69 (1.25–2.00); $P = 0.083$
13	Augustin 2015, Germany [11]	ICD-10 code (ischemic heart disease, I20[a] … I25[a])	0.08% vs. 0.06%. Prevalence (95% CI): 1.27 (0.18–9.07)

ICD: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CI: confidence interval; IQR: interquartile range; WtHR: waist-to-height ratio; SD: standard deviation; RHI: reactive hyperemia index; MACEs: major adverse cardiovascular events (including angina pectoris, myocardial infarction, and stroke).
[a] Severity of psoriasis definition: mild psoriasis = worst Physician's Global Assessment score 1 or 2, or 3 with body surface area ≤ 10%; severe = worst Physician's Global Assessment score 4 or 5, or 3 with body surface area > 10%.

Table 8
Chronologic links between child psoriasis and comorbidities.

No.	Studies	Events evaluated	Results, AOP vs. COP
3	De Jager 2010, Netherlands [17]	BMI in adulthood according to age at onset of psoriasis (COP/AOP); univariate analysis	Correlation between age at onset and BMI: r = 0.074; $P = 0.001$ Mean BMI in adulthood: 26.2 ± 4.8 kg/m^2 vs. 26.8 ± 4.5 kg/m^2; $P = 0.015$
4	Bryld 2010, Denmark [18]	Links between obesity and hospital admission for psoriasis in adulthood	High BMI in 12- to 13-year-old girls is associated with hospital admission for psoriasis in adulthood. Not found for males or younger girls
8	Mahé 2013, France [20]	Frequency of obesity, dyslipidemia, hypertension, diabetes, MACEs in adulthood according to age at onset of psoriasis (COP/AOP); multivariate analysis	No impact of age at onset of psoriasis on frequency of comorbidities in adulthood
10	Becker 2014, USA [24]	Chronologic link between overweight/obesity and psoriasis onset	Overweight or obesity precedes psoriasis by > 2 years in 93% of psoriatic children

BMI: body mass index; COP/AOP: childhood- (< 18 years)/adult-onset psoriasis; MACEs: major adverse cardiovascular events (including angina pectoris, myocardial infarction, and stroke).

any significant results in younger girls or in males, which suggests a statistical bias. Moreover, severe psoriasis is difficult to define in children: severity is based on the Psoriasis Area Severity Index (PASI) or body surface area (BSA), and the usual definition of moderate-to-severe psoriasis is a score > 10 on either scale, which has not been validated in children [44]. In contrast, Mahé et al. [20,26] reported no impact of age of onset of psoriasis on the frequency of obesity, diabetes, hypertension, dyslipidemia, or MACEs.

All these results suggest that a link may exist between overweight/obesity and childhood psoriasis. They also suggest that overweight could induce psoriasis, and thus that screening for psoriasis could be contributive in all overweight and obese children, although no studies have clearly demonstrated this. However, there is no confirmed link between childhood psoriasis and other comorbidities. Therefore, there is no justification for systematic screening for other comorbidities. However, since acitretin may induce hyperlipidemia, cyclosporine hypertension, and anti-TNF-alpha weight gain [45], screening for these comorbidities should be performed before initiation of these treatments for psoriasis. Moreover, there is no evidence for an impact of familial hypercholesterolemia screening in childhood on lipid concentration or cardiovascular outcome in adulthood, or for any long-term beneficial or adverse effect of beginning lipid-lowering treatment in childhood [46].

The present study had certain limitations. There was limited number of eligible studies, and the meta-analysis could not be performed due to the wide variability of definitions and methods.

5. Conclusion

Psoriasis in children is not associated with metabolic and cardiovascular comorbidities except overweight and obesity, for which higher prevalence is clearly demonstrated. Onset of psoriasis in childhood is not associated with higher risk of comorbidity in adulthood, but there seems to be a chronological link between overweight/obesity in childhood and psoriasis onset. Therefore, according to this systematic review of the literature, systematic screening is not warranted, but should be proposed for at-risk children: with obesity or family history of metabolic/cardiovascular disease.

Disclosure of interest

A. Badaoui and P. Tounian declare they have no conflict of interest concerning this article.

E. Mahé has been a consultant for Novartis, Abbvie, Boehringer Ingelheim, Celgene, Leo Pharma, and Janssen Cilag; has been an investigator for Amgen, Astra Zeneca, Abbvie, Boehringer Ingelheim, Celgene, Janssen Cilag, Leo Pharma, Novartis, and Pfizer, and has received speaker honoraria from Abbvie, Janssen Cilag, and Novartis.

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