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ORIGINAL ARTICLE

Psoriasis and cardiovascular disorders: association or epiphenomenon? Meta-analysis of observational studies

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Abstract

Psoriasis is a chronic inflammatory disease believed to be correlated with numerous cardiovascular risk factors including increased blood pressure, elevated blood cholesterol level, diabetes, inactivity, high body mass index (obesity) and dyslipidaemia. The present meta-analysis intends to assess the association between psoriasis and cardiovascular risk factors. Three hundred and fifty articles were primarily screened using NCBI MEDLINE/PubMed and Cochrane library from its inception until June 30, 2018. Of these, 26 observational studies depending upon the inclusion and exclusion criteria were included in the study with 17,672 psoriasis patients and 66,407 non-psoriasis subjects. The psoriasis patients were found to be at significantly increased risk of systolic blood pressure (SBP) [ORs 2.31 (95% CI 1.12, 4.74)], diastolic blood pressure (DBP) [ORs 2.31 (95% CI 1.58, 3.38)], abdominal obesity [ORs 1.90 (95% CI 1.45, 2.50)] and triglycerides [ORs 1.80 (95% CI 1.29, 2.51)] as compared to non-psoriasis subjects. The subgroup analyses of studies based on the continents revealed that psoriasis patients from Middle East are prone to higher risk factors of CVD including increased levels of triglyceride, cholesterol, DBP, SBP, fasting blood sugar, body mass index and decreased HDL levels, whereas psoriasis patients from European population reported increased LDL-C and waist circumference. The present study supports a significant association between psoriasis and incidence of major adverse cardiovascular events. Contrary to the previous literature, our finding suggests that hypertension is a highly associative condition in psoriasis. The findings of this study could be validated amongst well-defined cohorts of patients with psoriasis individually in different regions to confirm the implication of the study.

Keywords Psoriasis · Meta-analysis · CVD · Hypertension · Cholesterol · Obesity

Abbreviations

TGY	Triglycerides
HDL-C	High density lipoprotein-cholesterol
LDL-Cz	Low density lipoprotein-cholesterol
TC	Total cholesterol
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
BMI	Body mass index
WC	Waist circumference
SMD	Standardized mean difference
ORs	Odds ratio
CVD	Cardiovascular disorder

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Introduction

Psoriasis is an immune-mediated chronic inflammatory disease of the skin affecting nearly 2–3% of the world's population (Gisondi et al. 2010). The exact etiology of the disease is unknown; however, genetic susceptible markers and environmental predisposition are important during psoriasis pathogenesis (Aggarwal et al. 2017; Raimondo et al. 2018; Singh et al. 2019). Moreover, the immune system plays a crucial role in overall disease progression, with various innate and adaptive immune cells and pro-inflammatory mediators involved at different stages of the disease (Schiattarella et al. 2019). In recent years, various studies from different countries have shown that psoriasis is a systemic inflammatory disease, which is often associated with various comorbidities. In particular, there is a greater risk of developing severe vascular events such as cardiovascular and cerebrovascular diseases (Gelfand 2016; Furue et al. 2017; Takeshita et al. 2017).

Cardiovascular disease (CVD) refers to a number of heart conditions including atherosclerosis, heart attack, ischemic stroke, haemorrhagic stroke, arrhythmia and heart failure (Ma et al. 2014; Shah et al. 2017). The association between CVD and psoriasis could be ascribed to the pro-inflammatory molecules released during chronic inflammation (Mallbris et al. 2004). It has also been reported that treatments for psoriasis such as retinoids and cyclosporine may induce hyperlipidaemia that can promote future CVD (Grossman et al. 1991; Katz et al. 1999).

The available evidences present a controversial depiction of the risk of CVD in psoriasis patients. Numerous studies reported on the higher risk of CVD in psoriasis patients (Sommer et al. 2006; Tablazon et al. 2013; Richard et al. 2013; Karoli et al. 2013; Baeta et al. 2014; Parodi et al. 2014; Edson-Heredia et al. 2015). Furthermore, previous studies have shown increased mortality rates in psoriasis patients as compared to healthy controls (Mehta et al. 2010; Masson Regnault et al. 2017) and the life expectancy of patients with moderate to severe psoriasis is decreased by approximately 5 years, mainly due to cardiovascular comorbidities (Siegel et al. 2013). However, several reports (Piskin et al. 2003; Farshchian et al. 2007; Gelfand 2016) have elucidated that the risk of CVD, transient ischemic attacks, or cerebrovascular accidents remained unchanged between psoriatic patients and controls. Therefore, to answer these conflicting reports, we have performed a systematic review and meta-analysis of the association between psoriasis and cardiovascular risk factors. Depending on these results, the attributable cardiovascular risk was determined depending upon covariates such as region, study types, year of study and smoking behaviour.

Methodology

The criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed in conduction and reporting of the results of this systematic review and meta-analysis.

Search strategy

NCBI MEDLINE/PubMed and Cochrane library were primarily searched from inception until June 30, 2018, using combinations of the keywords: psoriasis and triglyceride, psoriasis and HDL, psoriasis and LDL, psoriasis and total cholesterol, psoriasis and systolic and diastolic blood pressure, psoriasis and fasting blood glucose, psoriasis and body mass index, psoriasis and waist circumference, psoriasis and dyslipidaemia, psoriasis and metabolic syndrome, psoriasis and comorbidities, psoriasis and cardiovascular disease. Other databases such as Google Scholar and Science Direct were also searched to identify the articles not indexed in the NCBI PubMed and Cochrane library. Additionally, the cross-references were also searched to identify additional eligible articles.

Selection criteria

The studies with following inclusion criteria were considered for the present meta-analysis: (1) studies provided original data; (2) study subjects were human adults with psoriasis and control group; (3) studies reported at least three or more parameters out of triglyceride (TGY), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), body mass index (BMI) and waist circumference (WC); (4) the study provided method description of various parameters with means and standard deviation. The exclusion criteria adopted were (1) studies reporting different parameters namely TGY, HDL-C, LDL-C, TC, SBP, DBP, FBG, BMI, WC with no numerical data; (2) studies reporting the discussed parameters on diseases other than psoriasis; (3) studies with reports on various discussed parameters only in psoriasis, without control group.

End points of cardiovascular risk factors

According to the National Cholesterol Education Program Adult Training Panel-III (NCEP ATP III) updated from 2005, a person is said to be under cardiovascular risk factor if (1) fasting glucose is 100 mg/dl or higher (or receiving drug therapy for hyperglycaemia), (2) blood pressure is

130/85 mmHg or higher (or receiving drug therapy for hypertension), (3) triglycerides are 150 mg/dl or higher (or receiving drug therapy for hypertriglyceridaemia), (4) high-density lipoprotein cholesterol complex (HDL-C) is less than 40 mg/dl in men or less than 50 mg/dl in women (or receiving drug therapy for reduced HDL-C), and (5) waist circumference is 102 cm (40 inches) or greater in men or 88 cm (35 inches) or greater in women; if Asian American, 90 cm (35 inches) or greater in men or 80 cm (32 inches) or greater in women.

Data extraction and study quality assessment

The included articles were thoroughly evaluated. Two review authors [SC] and [RP] extracted the data which were cross-checked by the third author [DP]. Extracted data included author's names, year of publication, region, means and SD level of age, TGY (Uyanik et al. 2002; Piskin et al. 2003; Farshchian et al. 2007, 2015; Akhyani et al. 2007; Dreiher et al. 2008; Balci et al. 2010; Choi et al. 2010; Langan et al. 2012; Vayá et al. 2013; Pehlevan et al. 2014; Akcali et al. 2014; Taheri Sarvtin et al. 2014; Parodi et al. 2014; Irimie et al. 2015; Barrea et al. 2016; Ražnatović-Đurović et al. 2016; Coban et al. 2016; Praveenkumar et al. 2016; Uczniak et al. 2016; Sharma et al. 2016; Kothiwala et al. 2016; Singh et al. 2017; Girisha and Thomas 2017; Milčić et al. 2017; Ganguly et al. 2018), HDL-C (Piskin et al. 2003; Farshchian et al. 2007, 2015; Akhyani et al. 2007; Dreiher et al. 2008; Balci et al. 2010; Choi et al. 2010; Langan et al. 2012; Vayá et al. 2013; Pehlevan et al. 2014; Akcali et al. 2014; Taheri Sarvtin et al. 2014; Parodi et al. 2014; Irimie et al. 2015; Barrea et al. 2016; Ražnatović-Đurović et al. 2016; Coban et al. 2016; Praveenkumar et al. 2016; Uczniak et al. 2016; Sharma et al. 2016; Kothiwala et al. 2016; Singh et al. 2017; Girisha and Thomas 2017; Milčić et al. 2017), LDL-C (Uyanik et al. 2002; Balci et al. 2010; Choi et al. 2010; Pehlevan et al. 2014; Irimie et al. 2015; Barrea et al. 2016; Coban et al. 2016; Singh et al. 2017), **TC** (Piskin et al. 2003; Balci et al. 2010; Langan et al. 2012; Akcali et al. 2014; Taheri Sarvtin et al. 2014; Parodi et al. 2014; Coban et al. 2016; Kothiwala et al. 2016; Singh et al. 2017; Milčić et al. 2017), SBP and DBP (Langan et al. 2012; Pehlevan et al. 2014; Akcali et al. 2014; Parodi et al. 2014; Farshchian et al. 2015; Barrea et al. 2016; Ražnatović-Đurović et al. 2016; Coban et al. 2016; Praveenkumar et al. 2016; Uczniak et al. 2016; Sharma et al. 2016; Kothiwala et al. 2016; Singh et al. 2017; Girisha and Thomas 2017; Milčić et al. 2017), FBG (Farshchian et al. 2007, 2015; Balci et al. 2010; Langan et al. 2012; Vayá et al. 2013; Pehlevan et al. 2014; Parodi et al. 2014; Barrea et al. 2016; Ražnatović-Đurović et al. 2016; Coban et al. 2016; Praveenkumar et al. 2016; Uczniak et al. 2016; Sharma et al. 2016; Kothiwala et al. 2016; Singh et al. 2017; Girisha and Thomas 2017; Milčić et al. 2017), BMI (Farshchian et al. 2007, 2015; Akhyani et al. 2007; Balci et al. 2010; Langan et al. 2012; Vayá et al. 2013; Pehlevan et al. 2014; Akcali et al. 2014; Taheri Sarvtin et al. 2014; Parodi et al. 2014; Barrea et al. 2016; Ražnatović-Đurović et al. 2016; Coban et al. 2016; Praveenkumar et al. 2016; Sharma et al. 2016; Kothiwala et al. 2016; Singh et al. 2017; Girisha and Thomas 2017; Milčić et al. 2017; Ganguly et al. 2018), WC (Vayá et al. 2013; Pehlevan et al. 2014; Akcali et al. 2014; Parodi et al. 2014; Barrea et al. 2016; Ražnatović-Đurović et al. 2016; Praveenkumar et al. 2016; Uczniak et al. 2016; Sharma et al. 2016; Kothiwala et al. 2016; Girisha and Thomas 2017; Milčić et al. 2017; Ganguly et al. 2018), and other relevant qualitative data are shown in Tables 1 and 2. The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality of the included studies. This scale allocates scores up to nine according to the assessment of selection, comparability of cases or controls, and ascertainment of exposure or outcome. Studies that received a score of ≥ 7 stars were judged as high quality.

Statistical analysis

In this meta-analysis, the mean and SD values of TGY, HDL-C, LDL-C, TC, SBP, DBP, FBG, BMI and WC were compared between psoriasis patients and controls. Standardized mean difference (SMD) and its 95% CI [UL, LL] in conjunction with odds ratio (ORs) was used as a summary statistic to measure the effect of various defined parameters. The overall effect size for SMD was presented as Z-score. The Z-score with a p value of ≤ 0.05 was considered statistically significant. Heterogeneity across studies was detected using I^2 statistics. Subgroup analysis was also performed to understand the prevalence of individual risk factors of metabolic syndrome among psoriasis patients and control. Meta-regression analysis was used to determine the effect of region, study type, smoking pattern and age-matched studies on various discussed parameters in psoriasis case and non-psoriasis control subjects. To assess the influence of individual study and result of the pooled estimate and to explain heterogeneity, a one-study removed sensitivity analysis was performed by excluding each study at a time. Risk of publication bias was adjudged using a funnel plot. All analyses were performed using Comprehensive Meta-analysis Version 3.3.070, USA.

Results

Literature search

The systematic search resulted in 350 relevant citations. Seventy-two articles were filtered for non-human models and, of the remaining 278 articles, only 55 full-text articles

Table 1 Demographic profile of studies included in the meta-analysis

S. no	Study	Year	Case population	Control population	Study type	Smoker	Region	Mean age of case (SD)	Mean age of control (SD)
1	Uyanik	2002	72	30	Case–control	No	Middle East	38.4 ± 4.7	38.4 ± 4.7
2	Piskin	2003	100	100	Case–control	No	Middle East	45.1 ± 16.4	44 ± 16.9
3	Farshchian	2007	30	30	Cross-sectional	No	Middle East	34.6 ± 11.47	34.63 ± 12.11
4	Akhyani	2007	50	50	Case–control	No	Middle East	41.82 ± 17.37	43.34 ± 20.73
5	Dreiher	2008	10,669	22,969	Cross-sectional	Yes	Middle East	57.8 ± 15.6	54.8 ± 17.9
6	Choi	2010	197	401	Case–control	Yes	Asia	45.04 ± 16.64	46.89 ± 14.62
7	Balci	2010	46	46	Cross-sectional	Yes	Middle East	39.5 ± 14.2	39.8 ± 13.5
8	Langan	2012	4065	40,650	Cross-sectional	No	Europe	45.74 ± 15.21	48.03 ± 13.77
9	Vaya	2013	91	101	Case–control	No	Europe	52.02 ± 13.56	50.6 ± 10.96
10	Akcali	2014	50	40	Cross-sectional	No	Middle East	38.6 ± 13.2	40.5 ± 14.6
11	Pehlevan	2014	59 s	82	Case–control	Yes	Middle East	46.8 ± 11.5	36.9 ± 11.5
12	Parodi	2014	390	344	Cross-sectional	Yes	Europe	52.9 ± 16	54.8 ± 18.1
13	Sarvtin	2014	50	50	Case–control	No	Middle East	43.8 ± 5.4	44.9 ± 7.1
14	Farshchian	2015	55	55	Case–control	Yes	Middle East	47.3 ± 18.4	45.16 ± 15.9
15	Irimie	2015	142	167	Case–control	Yes	Europe	49.51 ± 8.26	47.87 ± 16.43
16	Coban	2016	35	50	Prospective cohort	No	Middle East	44.43 ± 11.59	40.48 ± 13.47
17	Kothiwala	2016	140	140	Cross-sectional	Yes	Asia	37.9 ± 13.26	36.1 ± 11.63
18	Sharma	2016	100	100	Case–control	Yes	Asia	44.94 ± 11.1	43.28 ± 12.1
19	Uday	2016	30	30	Case–control	No	Asia	45.77 ± 12.09	42.07 ± 12.58
20	Djurovic	2016	101	126	Case–control	Yes	Europe	50 ± 14.39	43.7 ± 14.62
21	Uczniak	2016	246	75	Case–control	No	Europe	46 ± 13	46 ± 13
22	Barrea	2016	180	180	Cross-sectional	Yes	Europe	50 ± 11	48 ± 9
23	Singh	2017	334	230	Case–control	Yes	Asia	39.1 ± 14	35.4 ± 14.7
24	Milcic	2017	244	163	Cross-sectional	Yes	Europe	53.54 ± 15.16	43.69 ± 14.68
25	Girisha	2017	156	156	Case–control	Yes	Asia	45.5 ± 12.6	45.4 ± 12.5
26	Ganguly	2018	40	42	Case–control	No	Asia	44.83 ± 12.83	46.36 ± 10.11

The information about the case and control population of individual studies, region of the study, mean age of the case and control population and study setting

were screened for inclusion and exclusion criteria. Among 55 articles, only 26 articles were included in this meta-analysis (Fig. 1).

Description of studies and study quality assessment

Among the 26 included studies 84,079 subjects were enrolled, out of which 17,672 subjects were psoriasis patients (case) as compared to 66,407 non-psoriasis subjects (control). Various parameters, namely TGY, HDL-C, LDL-C, TC, SBP, DBP, FBG, BMI and WC were studied and are summarized in Tables 1 and 2. The details of the study quality included in the meta-analysis have been elucidated in Table 3.

Triglyceride levels

Mean and standard deviation of triglyceride levels in psoriasis patients and non-psoriasis subjects of 26 studies were pooled to give an estimate of overall effect. With high heterogeneity across studies ($I^2 = 98.5\%$), the random effect model was used to pool the effect size. Moderate and statistically significant spike in the effect of triglyceride level was evident in psoriasis patients. The pooled SMD (95% CI) was found to be 0.325 (0.141, 0.508) (sfig1a) which was statistically significant from the control ($p < 0.001$).

HDL levels

HDL levels were reported in 25 studies. With substantially high heterogeneity across the studies ($I^2 = 99.016\%$), the random effect model was used. The result based on the model showed lowered HDL levels, SMD (95% CI) – 0.081 (–0.323, 0.161) (sfig1b) was recorded in psoriasis patients. The SMD value for HDL-C depicts that impaired level of HDL-C is not an associative cardiovascular risk factor in psoriasis patients.

Table 2 Individual level of reported parameters in studies included in the meta-analysis

Study	Year	BMI		FBS		Systolic BP		Diastolic BP		Triglyceride	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Uyanik	2002	NM	NM	NM	NM	NM	NM	NM	NM	150.13 ± 25.86	115.05 ± 21.78
Piskin	2003	NM	NM	NM	NM	NM	NM	NM	NM	130.68 ± 67.59	111.65 ± 47.38
Farshchian	2007	22.96 ± 4.23	23.23 ± 3.08	95.36 ± 12.38	92 ± 11.28	NM	NM	NM	NM	121.63 ± 54.56	127.03 ± 65.39
Akhyani	2007	25.56 ± 2.26	25.2 ± 2.39	NM	NM	NM	NM	NM	NM	140.3 ± 55.24	115.84 ± 47.28
Dreiher	2008	NM	NM	NM	NM	NM	NM	NM	NM	148.8 ± 15.6	139.3 ± 86.1
Choi	2010	NM	NM	NM	NM	NM	NM	NM	NM	152.17 ± 76.44	119.16 ± 70.32
Balci	2010	26.5 ± 4.2	26.8 ± 4.1	101.8 ± 43.5	83.4 ± 9.1	NM	NM	NM	NM	139.7 ± 129.9	119.1 ± 74.2
Langan	2012	27.1 ± 1.87	28.4 ± 1.12	97.2 ± 6.66	100.8 ± 7.56	144 ± 8	149 ± 8.25	90 ± 5	90 ± 4.5	150.57 ± 30.99	168.28 ± 35.43
Vaya	2013	28.9 ± 5.4	26.2 ± 3.9	104 ± 33	97 ± 17	NM	NM	NM	NM	152 ± 121	101 ± 50
Akcali	2014	26.92 ± 4.11	25.73 ± 5.89	110.92 ± 57.58	95.66 ± 37.63	130 ± 17	120 ± 15	83 ± 14	77 ± 11	177.43 ± 173.91	146.17 ± 84.93
Pehlevan	2014	29 ± 4.7	27 ± 5.6	101 ± 32	93.6 ± 18.8	122.7 ± 12.8	113.5 ± 16.4	81 ± 9	70 ± 16.6	142 ± 94	101 ± 52
Parodi	2014	27.3 ± 4.8	25.5 ± 4.2	98.3 ± 25	92.8 ± 24	128.6 ± 14	126.3 ± 12.7	79.4 ± 9.6	77.3 ± 8.6	126.4 ± 69.8	108.7 ± 61.3
Sarvtin	2014	24.4 ± 2.2	23.8 ± 2.3	NM	NM	NM	NM	NM	NM	156.3 ± 56.1	117 ± 41.8
Farshchian	2015	26.36 ± 4.71	24.6 ± 3	101 ± 25.7	96 ± 14.4	135.83 ± 19	118.1 ± 16	81.11 ± 11.3	74.04 ± 10.9	152.6 ± 72	107.05 ± 35
Irimie	2015	NM	NM	NM	NM	NM	NM	NM	NM	163.21 ± 56.72	109.47 ± 45.29
Coban	2016	27.18 ± 4.8	26.88 ± 4.28	106.11 ± 45.37	93.64 ± 11.77	121.57 ± 14.39	118.5 ± 9.8	79 ± 12.11	74 ± 8.3	134.83 ± 62.46	136.74 ± 137.3
Kothiwala	2016	24 ± 4.43	22.6 ± 3.71	98.5 ± 16.82	91.1 ± 12.82	129.4 ± 14.42	121.5 ± 11.9	82.3 ± 9.3	77.8 ± 9.14	130.2 ± 69.83	142.3 ± 102.88
Sharma	2016	24.42 ± 3.96	23.91 ± 3.66	103.44 ± 32.46	90.95 ± 16.29	125.43 ± 11.01	121.98 ± 9.67	80.83 ± 7.17	78.32 ± 6.7	156.89 ± 58.47	133.34 ± 29.85
Uday	2016	24.56 ± 4.76	24.23 ± 3.91	134.17 ± 60.04	118.4 ± 41.78	122.86 ± 14.97	121.66 ± 14.85	80.86 ± 11.68	78.88 ± 12.67	120.5 ± 23.81	145 ± 24.31
Djurovic	2016	26.81 ± 3.17	25.45 ± 5.12	97.2 ± 21.6	86.22 ± 14.94	146.19 ± 18.88	119 ± 11.01	93.56 ± 9.96	75.29 ± 8.4	116.03 ± 47.83	131.97 ± 92.11
Uczniak	2016	NM	NM	96.71 ± 16.02	92.64 ± 13.17	135.06 ± 12.82	128.8 ± 9.6	83.26 ± 6.16	83 ± 6.92	145.68 ± 29.95	110.92 ± 28.83
Barrea	2016	30.2 ± 6.1	29.6 ± 7.3	105 ± 33	96 ± 32.5	130 ± 16.25	125 ± 17.5	80 ± 12.5	75 ± 12.5	164 ± 91.5	139 ± 51.75
Singh	2017	24.8 ± 5.1	23.1 ± 4.4	89.7 ± 21.2	85.7 ± 11.4	125.8 ± 14.5	119.5 ± 11.8	80.4 ± 8.8	77.7 ± 7.5	151.2 ± 78	133.3 ± 52.5
Milcic	2017	27.15 ± 4.87	25.45 ± 4.89	92.88 ± 36.54	87.12 ± 24.48	132.08 ± 17.59	119 ± 11.61	80.62 ± 10.62	75.04 ± 8.27	147.03 ± 79.65	126.55 ± 85.84
Girisha	2017	24 ± 4.8	25.2 ± 2.2	97.07 ± 14.7	97.01 ± 15.78	124.26 ± 13.17	124.76 ± 13.27	81.48 ± 6.77	80.62 ± 7.34	138.49 ± 38.98	129.78 ± 31.26
Ganguly	2018	24.12 ± 3.48	23.75 ± 3.79	NM	NM	NM	NM	NM	NM	158.4 ± 125.53	125.93 ± 53.01

Study	Year	Total cholesterol		LDL-cholesterol		HDL		Waist circumference	
		Case	Control	Case	Control	Case	Control	Case	Control
Uyanik	2002	161.44 ± 43.23	145.79 ± 31.67	49.73 ± 10.69	45.16 ± 10.42	37.97 ± 10.015	42.03 ± 8.24	NM	NM
Piskin	2003	NM	NM	NM	NM	47.3 ± 10.68	48.8 ± 13.4	NM	NM
Farshchian	2007	NM	NM	NM	NM	37.3 ± 4.96	35.5 ± 4.17	NM	NM
Akhyani	2007	NM	NM	NM	NM	39.64 ± 7.91	41.32 ± 7.73	NM	NM
Dreiher	2008	NM	NM	NM	NM	48.3 ± 12.9	49.9 ± 13.4	NM	NM
Choi	2010	187.01 ± 38.26	187.4 ± 32.7	105.11 ± 32.81	109.41 ± 29.45	52.66 ± 11.68	53.02 ± 13.57	NM	NM

Table 2 (continued)

Study	Year	Total cholesterol		LDL-cholesterol		HDL		Waist circumference	
		Case	Control	Case	Control	Case	Control	Case	Control
Balci	2010	178.8 ± 36.6	170.1 ± 39	107.8 ± 34.4	103.4 ± 355.6	43.6 ± 10.5	42.1 ± 11.6	NM	NM
Langan	2012	NM	NM	NM	NM	132.85 ± 13.28	123.99 ± 10.62	NM	NM
Vaya	2013	215 ± 41	218 ± 32	NM	NM	55 ± 13	60 ± 14	99.86 ± 13.7	92.39 ± 12.3
Akcali	2014	NM	NM	NM	NM	41.69 ± 10.5	43.88 ± 10.76	97.2 ± 10.48	94.44 ± 11.07
Pehlevan	2014	196 ± 47	184 ± 44	119 ± 36	113 ± 37	51 ± 15	52 ± 14	94 ± 13	93 ± 14
Parodi	2014	201.3 ± 40	193.1 ± 40.1	NM	NM	49.4 ± 13.8	53.8 ± 14.5	95.4 ± 17.7	88.6 ± 15.3
Sarvtin	2014	NM	NM	NM	NM	47.6 ± 8.8	53.8 ± 6.6	NM	NM
Farshchian	2015	NM	NM	NM	NM	66 ± 10.4	49 ± 9	NM	NM
Irimie	2015	223.42 ± 142.72	204.3 ± 82.51	118.62 ± 36.79	104.26 ± 31.86	44.63 ± 11.39	52.46 ± 8.65	NM	NM
Coban	2016	194.43 ± 43.65	176.44 ± 36.22	119.71 ± 34.83	102.94 ± 30.78	48.48 ± 10.81	47.92 ± 14.1	NM	NM
Kothiwala	2016	NM	NM	NM	NM	42.4 ± 6.79	42.2 ± 5.46	89.7 ± 11.92	83.6 ± 9.22
Sharma	2016	NM	NM	NM	NM	42.77 ± 12.46	42.91 ± 6.23	83.47 ± 10.27	83.04 ± 8.02
Uday	2016	NM	NM	NM	NM	38.93 ± 10.53	37.77 ± 11.03	89.28 ± 11.77	85.36 ± 8
Djurovic	2016	NM	NM	NM	NM	91.22 ± 36.31	118.68 ± 38.97	88.98 ± 13.01	85.63 ± 13.7
Uczniak	2016	NM	NM	NM	NM	58.74 ± 14.56	58.17 ± 13.49	97.03 ± 13.71	92 ± 14.42
Barrea	2016	197.5 ± 54.5	171 ± 57.5	132.6 ± 44.7	121.7 ± 51.8	43.3 ± 11	45.7 ± 7.9	109.6 ± 21.65	95.7 ± 22.85
Singh	2017	176.8 ± 38	168.1 ± 35.6	111.9 ± 30.6	106.6 ± 30.1	45.7 ± 9.3	45.8 ± 10.7	NM	NM
Milcic	2017	NM	NM	NM	NM	45.24 ± 11.99	52.2 ± 16.24	95.4 ± 13.62	84.54 ± 13.62
Girisha	2017	NM	NM	NM	NM	44.42 ± 9.02	46.53 ± 7.7	86.27 ± 13.14	87.35 ± 31.26
Ganguly	2018	NM	NM	NM	NM	NM	NM	86.47 ± 8.9	85.17 ± 10.45

The mean and standard deviation value of different parameters reported in the individual study. NM implies not mentioned

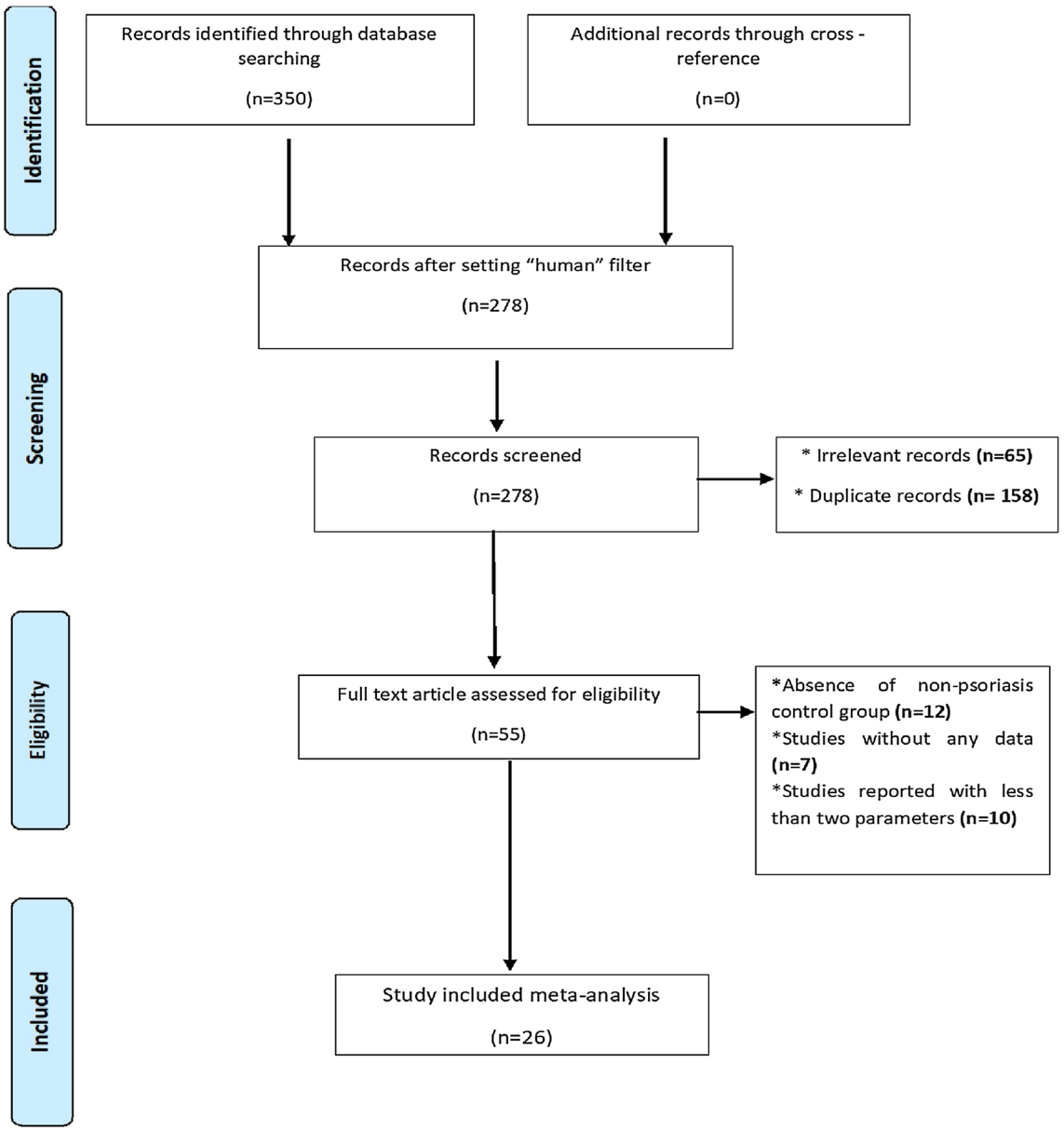

Fig. 1 Schematic representation of the study selection process. Different databases were screened with suitable keywords to retrieve relevant records. Using the inclusion and exclusion criteria, 26 studies were finally selected for study

LDL levels

Eight studies reported the mean and SD values for LDL levels**.** The measured heterogeneity (I^2) was found to be 81.68%; hence, the random effect model was used. The overall SMD (95% CI) was calculated to be 0.215 (0.070, 0.360) (sfig1c). The result depicted moderately increased LDL levels in psoriasis patients as compared to the control population with statistically significant p value < 0.05.

Total cholesterol levels

Mean and SMD values of ten studies were used to comprehend the total cholesterol levels. The measured heterogeneity between trials ($I^2 = 45.75\%$) was recorded. Based upon the random effect model, the overall SMD (95% CI) was estimated to be 0.276 (0.190, 0.363) (sfig1d) and the difference from the control was significant ($p < 0.001$).

Table 3 Quality assessment of studies included in the meta-analysis

S. no	Study	Year	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for both groups	Overall NOS scores
1	Uyanik	2002	*	*	*	*	**	*	*	8
2	Piskin	2003	*	*	*	*	*	*	*	7
3	Farshchian	2007	*	*	*	*	**	*	*	8
4	Akhyani	2007	*	*	*	*	**	*	*	8
5	Dreiher	2008	*	*	*	*	**	*	*	8
6	Choi	2010	*	*	*	*	*	*	*	7
7	Balci	2010	*	*	*	*	**	*	*	8
8	Langan	2012	*	*	*	*	**	*	*	8
9	Vaya	2013	*	*	*	*	**	*	*	8
10	Akcali	2014	*	*	*	*	**	*	*	8
11	Pehlevan	2014	*	*	*	*	**	*	*	8
12	Parodi	2014	*	*	*	*	**	*	*	8
13	Sarvtin	2014	*	*	*	*	**	*	*	8
14	Farshchian	2015	*	*	*	*	**	*	*	8
15	Irimie	2015	*	*	*	*	*	*	*	7
16	Coban	2016	*	*	*	*	**	*	*	8
17	Kothiwala	2016	*	*	*	*	*	*	*	7
18	Sharma	2016	*	*	*	*	**	*	*	8
19	Uday	2016	*	*	*	*	*	*	*	7
20	Djurovic	2016	*	*	*	*	**	*	*	8
21	Uczniak	2016	*	*	*	*	**	*	*	8
22	Barrea	2016	*	*	*	*	*	*	*	7
23	Singh	2017	*	*	*	*	*	*	*	7
24	Milcic	2017	*	*	*	*	**	*	*	8
25	Girisha	2017	*	*	*	*	**	*	*	8
26	Ganguly	2018	*	*	*	*	*	*	*	7

Systolic and diastolic blood pressure levels

Fifteen studies reported systolic and diastolic blood pressure levels. High heterogeneity ($I^2 = 98.54\%$ and $I^2 = 94.45\%$) was noticed across the studies for systolic and diastolic blood pressure levels, respectively. The effect size was measured using random effect model. The pooled SMD (95% CI) for diastolic blood pressure levels was found to be 0.463 (0.254, 0.672) (sfig1e) and the difference from the control was significant at $p < 0.05$, whereas the pooled SMD (95% CI) for systolic blood pressure was 0.462 (0.065, 0.859) (sfig1f) and the difference from control was significant at $p < 0.01$. The increased SMD for both SBP and DBP indicates that hypertension is the most associative CVD risk factor among psoriasis patients.

Fasting blood glucose

Fasting blood glucose level was studied in 18 works. Owing to high heterogeneity ($I^2 = 96.46\%$), the random effect model was used for assessing the effect size. The pooled SMD (95% CI) for fasting blood glucose was 0.270 (0.023, 0.517) (sfig1g) and the difference from control was significant at $p < 0.05$.

BMI levels

Mean and SD values of 20 studies were considered to draw the comparison between the body mass index in the psoriasis case and non-psoriasis control. Across the studies, heterogeneity was significant ($I^2 = 98.68\%$); hence, the random effect model was used. The estimated SMD (95% CI) for BMI was found to be 0.136 (– 0.260, 0.533) (sfig1h) with non-significant difference from control ($p > 0.05$). However; the calculated SMD does not present a clear picture of its association.

Waist circumference

Waist circumference level was interpreted from the analysis of 13 studies. Across the studies, the heterogeneity was significant ($I^2 = 76.29\%$); hence, the random effect model was chosen. The overall SMD, 95% CI (UL, LL) for waist circumference was estimated to be 0.356 (0.206, 0.506) (sfig1i) with a significant difference from control. The increased waist circumference depicts a closer association with psoriasis patients.

Subgroup analyses

Subgroup analysis was performed by region, i.e. Asia, Europe and Middle East for selected metabolic factors to reduce the heterogeneity among studies (Table 4).

Eleven studies from the Middle East, 8 from Asia and 7 from Europe reported that the increased incidence of triglyceride level was highest in the Middle East region (SMD 0.429 [95% CI 0.206, 0.651]), followed by European population (SMD 0.333[95% CI 0.184, 0.851]) and subsequently in Asian residents (SMD 0.203 [95% CI 0.024, 0.43]). The HDL-C level was assessed for 11 Middle Eastern studies, 6 Asian and 8 studies from the European region. The SMD in all the three regions was found to be insignificant, i.e. a similar pattern of HDL level was found among psoriasis patient across the region. Two European, two Asian and four studies from the Middle East region depending on heterogeneity used random effect model to estimate the incidence of increased LDL level. LDL level was significantly higher among psoriasis patients from the European population (SMD 0.317 [95% CI 0.127, 0.507], $p < 0.001$). The LDL level in psoriasis patients from Middle East and Asia was not an associative condition in the populations. Four studies from the Middle East reported maximum and significant difference in total cholesterol (TC) levels (SMD 0.323 [95% CI 0.124, 0.521], $p < 0.001$) among psoriasis patients compared to the other two regions of Europe and Asia.

On the basis of the random effect model, six European, five Asian and four studies from the Middle East population were assessed for increased blood pressure levels. Apparently, the value of difference was highest and statistically significant for both SBP (SMD 0.632 [95% CI 0.344, 0.921]) and DBP (SMD 0.621 [95% CI 0.425, 0.818]) in the Middle East population. Both Middle East and Asian populations reported blood pressure as an associative condition in psoriasis patients; however, it was not found to be significantly involved in the European group. A similar result was found for FBS level among the psoriasis population. The difference in FBS level among psoriasis patients was found to be statistically significant at $p < 0.001$ from Middle East (SMD 0.347 [95% CI 0.181, 0.512]) and Asian countries (SMD 0.292 [95% CI 0.098, 0.485]). Eight Middle East studies reported a higher incidence of increased BMI (SMD 0.205 [95% CI 0.063, 0.347]). Increased waist circumference was found as a distinctive pattern among six studies from the European population with SMD = 0.508 [95% CI 0.348, 0.667].

Effect of drug treatment on psoriasis patients

Three studies (Dreiher et al. 2008; Choi et al. 2010; Pehlevan et al. 2014) considered in the present meta-analysis included 10,925 psoriasis patients on drug treatment with cyclosporine, acitretin, methotrexate, immune-modulators or any other steroidal therapy and 23,452 non-psoriasis patients. Meta-analysis of these studies revealed a moderate impact on TGY (0.198 [0.068, 0.098]) and TC (0.136[0.023,

Table 4 Summary of subgroup analysis of various parameters

Parameters	Overall estimate	Region	*n*	SDM	LL	UL	*z* value	*p* value
TGY	0.325 (0.141, 0.508)	a Europe	7	0.333	−0.184	0.851	1.262	0.207
		b Middle East	11	**0.429**	0.206	0.651	3.774	< 0.001
		c Asia	8	0.203	−0.024	0.43	1.75	0.08
HDL	−0.081 (−0.323, 0.161)	a Europe	8	−0.258	−0.848	0.331	−0.86	0.39
		b Middle East	11	**0.019**	−0.243	0.28	0.141	0.888
		c Asia	6	−0.044	−0.134	0.045	−0.0973	0.33
LDL	0.215 (0.070, 0.360)	a Europe	2	**0.317**	0.127	0.507	3.26	0.001
		b Middle East	4	0.262	0.044	0.479	2.36	0.018
		c Asia	2	0.017	−0.291	0.326	0.11	0.913
TC	0.276 (0.190, 0.363)	a Europe	4	0.205	0.012	0.399	2.084	0.037
		b Middle East	4	**0.323**	0.124	0.521	3.19	0.001
		c Asia	2	0.112	−0.219	0.353	0.911	0.362
DBP	0.463 (0.254, 0.672)	a Europe	6	0.522	0.135	0.909	2.646	0.008
		b Middle East	4	**0.621**	0.425	0.818	6.206	< 0.001
		c Asia	5	0.309	0.18	0.437	4.717	< 0.001
SBP	0.462 (0.065, 0.859)	a Europe	6	0.498	−0.185	1.18	1.43	0.153
		b Middle East	4	**0.632**	0.344	0.921	4.29	< 0.001
		c Asia	5	0.308	0.062	0.554	2.454	0.014
FBS	0.270 (0.023, 0.517)	a Europe	7	0.185	−0.208	0.578	0.921	0.357
		b Middle East	6	**0.347**	0.181	0.512	4.11	< 0.001
		c Asia	5	0.292	0.098	0.485	2.959	0.003
BMI	0.136 (−0.260, 0.533)	a Europe	6	0.105	−0.681	0.891	0.262	0.793
		b Middle East	8	**0.205**	0.063	0.347	2.836	0.005
		c Asia	6	0.12	−0.13	0.369	0.939	0.347
WC	0.356 (0.206, 0.506)	a Europe	6	**0.508**	0.348	0.667	6.239	< 0.001
		b Middle East	2	0.145	−0.116	0.406	1.09	0.276
		c Asia	5	0.211	−0.064	0.485	1.506	0.003

0.072]) indicating that steroidal treatment might contribute to dyslipidaemia among psoriasis patients. Further analysis was conducted excluding these three studies to assess the occurrence of CVD in psoriasis patients. The analysis indicated moderate to significant impact of TC (0.242 [0.128, 0.356]) and TGY (0.317[0.052, 0.582]). Hence, it can be interpreted that cardiovascular risk factors are precursors for psoriasis patients and the drugs used in the disease treatment also contribute to elevated triglyceride and total cholesterol levels.

Meta-regression

Meta-regression analysis was performed to assess the association of mean difference of triglyceride levels, HDL levels, LDL levels, total cholesterol levels, systolic and diastolic blood pressure, fasting blood glucose, body mass index, waist circumference in psoriasis case vs non-psoriasis subjects with other covariates such as region, study types, year of study and smoking behaviour. No significant relationship was found in the mean difference of the defined parameters by any of the selected covariates independently. Within the study, the test of statistics showed that the association between differences in mean and selected covariates were again confirmed as insignificant in a linear model by weighing each study (Q test statistics for each covariate, $p > 0.05$). However, the test of heterogeneity between and within the study for each covariate was found to be significant for all defined levels.

Publication bias and sensitivity analysis

Publication bias was estimated for all included studies in this meta-analysis. From visualization of funnel plot, we confirmed the presence of biasness (Fig. 2). We confirmed the same using Egger's regression test with biasness between studies at $p < 0.05$ with 95% CI [−0.545, 6.453]. Studies with larger than average effects are more likely to be published, and this might lead to an upward bias in the summary effect.

Sensitivity analysis by emitting a single study in each turn showed the pooled SMD of total triglyceride levels, HDL levels, LDL levels, total cholesterol levels, systolic and diastolic blood pressure, fasting blood glucose, body mass

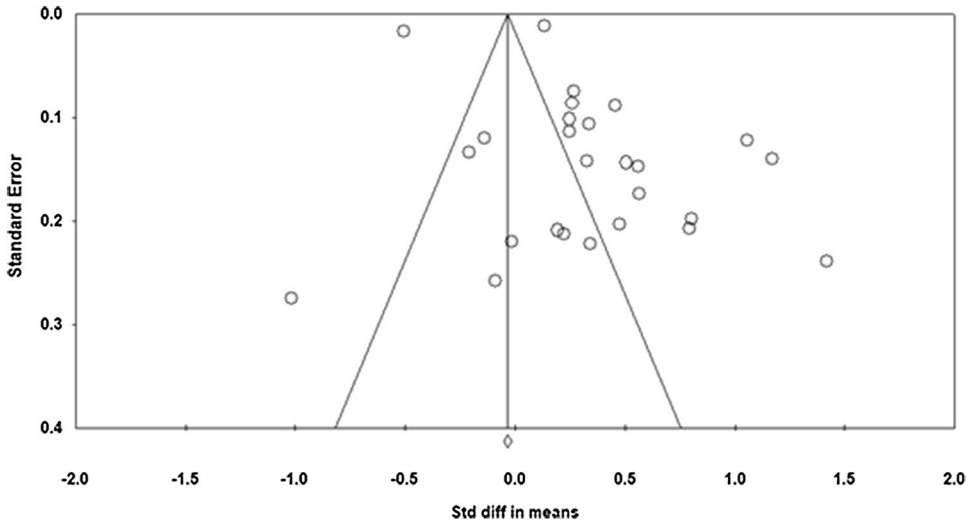

Fig. 2 Funnel plot for studies included in the meta-analysis

index and waist circumference. After emitting each study no difference in overall standard mean difference was found stating that the overall effect sizes were reliable.

Discussion

The conflicting literature associating psoriasis with cardiovascular risk factors is the cornerstone for this study. Psoriasis, which was once believed to be limited to the skin, is presently being studied and diagnosed with multidimensional medical conditions. In this meta-analysis, we analysed several individual cardiovascular risk factors including triglyceride, HDL-C, LDL-C, total cholesterol, SBP, DBP, BMI and waist circumference among psoriasis patients in comparison to non-psoriasis control subjects. Among these defined risk factors, our study reported increased levels of SBP (0.462 [0.065, 0.859]), DBP (0.463 [0.254, 0.672]), waist circumference (0.356 [0.206, 0.506]), triglycerides (0.325 [0.141, 0.508]) and FBS (0.270 [0.023, 0.517]) as highly associative risk factors in psoriasis patients. Apart from these, increased level of TC (0.276 [0.19, 0.363]), LDL-C (0.215 [0.070, 0.360]) and BMI (0.136 [–0.260, 0.533]) are moderately prevalent risk factors among patients. However, the role of lowered HDL-C (–0.081 [–0.323, 0.161]) as an associative risk factor remains inconclusive.

The result of the present meta-analysis indicates increased levels of SBP and DBP resulting in hypertension which is in concordance with a meta-analysis by Miller et al. (2013), Armstrong et al. (2011) and Armesto et al. (2012) who reported an analogous association with OR [95% CI] 1.8 [1.6, 2.0], 1.58 [1.42, 1.76] and 1.60 [1.24, 2.05], respectively. However, Cohen et al. (2010) and Langan et al. (2012) suggested a significantly weak association between the two with respective pooled ORs [95% CI] as 1.37 [1.29, 1.46] and 1.20 [1.11, 12.9].

It is interesting to note that increased waist circumference was a highly associative risk factor among psoriasis patients [SMD 0.356, 95% CI 0.206, 0.506]; however, increased BMI was moderately associated 0.136[95% CI -0.260, 0.533] in psoriasis patients. In earlier reports, BMI was found to be a more closely related risk factor as reported by Miller et al. (2013), who found obesity based on abdominal fat 1.6 [95% CI 1.2, 2.3] and obesity based on body mass index OR 1.8 [95% CI 1.4, 2.2]. Setty et al. (2007) found the multivariate relative risks (RR) of psoriasis were 1.40 [95% CI 1.13, 1.73] for a BMI of 25.0—29.9; 1.48 [95% CI 1.15, 1.91] for a BMI of 30.0—34.9; and 2.69 [95% CI 2.12, 3.40] for a BMI of 35.0 or greater. Kumar et al. (2013) reported a higher incidence of increased waist circumference in psoriasis patients from the USA with risk ratio 1.63 (95% CI 1.24, 2.14).

The components of dyslipidaemia may include elevated LDL cholesterol, triglycerides, and/or low HDL (protective) cholesterol. These components may occur singly or, more often, in clusters of two or all three. Our study reported standard mean difference [95% CI] for triglyceride, total cholesterol, LDL-C and HDL-C as 0.325[0.141, 0.508], 0.276[0.19, 0.363], 0.215[0.070, 0.360] and – 0.081[– 0.323–0.161], respectively. Among these components, we could not establish any existing relationship of lowered HDL-C as a risk factor in psoriasis patients. Despite several studies suggesting impaired serum levels of lipids and lipoproteins as an important risk factor for CVD among psoriasis patients, many of the reports remain controversial (Farshchian et al. 2007; Toker et al. 2009; Ma et al. 2014). However, our result was found to be in agreement with Cohen et al. (2010), who reported 48.6% dyslipidaemia in psoriasis patients in comparison to 37.9%

in control subjects at $p < 0.001$. In a systematic review, 20 of 25 included studies found significant associations between psoriasis and dyslipidaemia, with ORs ranging from 1.04 to 5.55 (Ma et al. 2014). Miller et al. (2013) in a meta-analysis found association of dyslipidaemia in psoriasis patients at OR 1.5 (95% CI 1.4, 1.7).

The present study establishes increased blood sugar level as an important risk factor in psoriasis patients with measured SMD (95% CI) 0.27 [0.023, 0.517]. The estimate corresponds to the findings of Khalid et al. (2013) on Danish cohorts who estimated the incidence rate ratio (IRR) of diabetes mellitus was increased in all patients with psoriasis, IRR 1.49 [95% CI 1.43, 1.56], and Lee et al. (2014) reported the condition of diabetes mellitus as being prevalent in psoriasis patients with hazard ratio [95% CI] 1.35[1.11,1.65].

The individual risk factors of cardiovascular disease were also studied according to the different geographical locations of Europe, Asia and Middle East. In all, 8 European studies, 2 each from Serbia and Italy, 1 each from Spain, Poland, Romania and the UK; 7 Asian studies, 1 from South Korea and 6 from India; and 11 studies from the Middle East, including 6 from Turkey, 4 from Iran and 1 from Israel, were involved in the present study. The present study conveyed that different cardiovascular disease markers, reportedly elevated triglyceride, total cholesterol, diastolic blood pressure, systolic blood pressure, fasting blood sugar and body mass index, were highest among the Middle East region. The association was found to be statistically significant, other than HDL levels. Our result is in accordance with reports of several authors including Al-Mutairi et al. (2010) who reported higher odds of inflammatory arthritis, coronary heart disease, obesity, diabetes mellitus II, hypertension and dyslipidaemia among psoriasis patients of Kuwait. Dreiher et al. (2008) reported that prevalence of dyslipidaemia was significantly higher in psoriasis patients, OR 1.48 [95% CI 1.40,1.55]. Zindancı et al. (2012) reported that diabetes mellitus and hypertension accompanying in psoriasis patients along with MS in the Turkish population. In our subgroup analysis, increased LDL and obesity by waist circumference were found to be more associative with the European population. Our result agrees with the meta-analysis of Armstrong et al. (2012) who reported the prevalence of obesity in the same population with OR 1.66 [95% CI 1.46–1.89]. Love et al. (2011) also reported abdominal obesity to be associated with the European population with odds of 1.72 [1.03–2.86].

It is also interesting to note that the present psoriasis treatment regimen is associated with cardiovascular risk factors and cardiovascular disorders. Several authors including Hu and Lan (2017), Abuabara et al. (2011) and Prodanovich et al. (2009) in their study on American cohorts reported use of several systemic immunomodulatory therapies in psoriasis patients resulting in increased hypertension, dyslipidaemia and myocardial infarction. The present meta-analysis also points to the association of psoriasis drugs and cardiovascular risk factors. Likewise, Kim et al. (2017), Ahlehoff et al. (2015), Lan et al. (2012) and Chin et al. (2013) also stated the presence of hypertension and dyslipidaemia in psoriasis patients on treatment with methotrexate and retinoid.

In the wake of the reported results and existing literature it becomes extensively important to understand the shared molecular mechanisms responsible for the association between psoriasis and cardiovascular comorbidities. Genome-wide association studies have found the increased inheritance of certain common genetic variants, HLA, FUT2 and UBE2L3, SH2B3, to be associated with cardiovascular risk in patients with psoriasis, indicating shared genetic factors (Lu et al. 2013). Moreover, this association can be discussed in the context of common inflammatory pathways. Karbach et al. (2014) and Owczarczyk-Saczonek and Placek (2017) explained that the overexpression of Th17 cytokines (IL-17, IL-6 and IL-8) may intercede vascular inflammation and the development of atherosclerosis and cardiovascular comorbidities in patients with psoriasis. However, the temporal relationship between psoriatic systemic inflammation and cardiovascular disease remains unclear. It is possible that the systemic inflammation of psoriasis may lead to the development of cardiovascular diseases, or alternatively the cardiovascular risk factors may cause immune dysfunction leading to psoriasis. In the theory known as the "psoriatic march", it is proposed that psoriasis may induce systemic inflammation leading to insulin resistance, endothelial dysfunction, and development of atherosclerosis and cardiovascular comorbidities (Boehncke et al. 2011).

The strength of this study is inclusion of studies with incidence (not prevalence) of cardiovascular risk factors. We have also stratified the studies into different regions to get a concise picture of cardiovascular incidences among psoriasis patients. Additionally, we also performed meta-regression analysis to assess the association of cardiovascular risk factors in psoriasis case and non-psoriasis subjects with other covariates such as region, study types, year of study and smoking behaviour.

Conclusion

To conclude, the present meta-analysis study was carried out to understand whether psoriasis has any association with cardiovascular risk factor or not. Our results support a significant association between psoriasis and incidence of major adverse cardiovascular events. While the previous literature reported moderate association between

hypertension and psoriasis, our findings suggest that hypertension is a highly associative condition in psoriasis. It is noteworthy that the incidence of cardiovascular events among psoriasis patients is dominant in the Middle East population as compared to other geographic locations considered in the present study. This occurrence may be related to variations in genetic structure, environmental exposures, or issues related to health-care use. Patients with psoriasis should be educated regarding the increased risk of cardiovascular disease and aggressively treated for modifiable cardiovascular risk factors. Moreover, it would be best to conduct a study using homogenous designs and sample size to reduce heterogeneity and variability and to get a more precise information of the association between cardiovascular risk factors and psoriasis. The findings of this study could be validated amongst well-defined cohorts of patients with psoriasis individually in different regions to confirm the implication of the study.

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Authors' contribution Saumya Choudhary, Rachna Patel, Dibyabhaba Pradhan: acquisition of data. Saumya Choudhary, Rachna Patel, Dibyabhaba Pradhan: analysis or interpretation of data. All authors: concept or design, drafting of the manuscript and critical revision.

Compliance with ethical standards

Conflict of interest The authors declare there are no competing interests.

Ethical approval The present meta-analysis is exempted from ethical approval, as data were obtained from previous studies in which informed consent was already obtained by the trial investigator, and the present analysis will be addressing similar questions to the research question for which the data were collected.

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