Monocyte-to-High-Density Lipoprotein Ratio Is Associated with Systemic Inflammation, Insulin Resistance, and Coronary Subclinical Atherosclerosis in Psoriasis: Results from 2 Observational Cohorts

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Systemic inflammation or insulin resistance drive atherosclerosis. However, they are difficult to capture for assessing cardiovascular risk in clinical settings. The monocyte-to-high-density lipoprotein ratio (MHR) is an accessible biomarker that integrates inflammatory and metabolic information and has been associated with poorer cardiovascular outcomes. Our aim was to evaluate the association of MHR with the presence of subclinical atherosclerosis in patients with psoriasis. The study involved a European and an American cohort including 405 patients with the disease. Subclinical atherosclerosis was assessed by coronary computed tomography angiography. First, MHR correlated with insulin resistance through homeostatic model assessment for insulin resistance, with high-sensitivity CRP and with ^{18}F-fluorodeoxyglucose uptake in spleen, liver, and bone marrow by positron emission tomography/computed tomography. MHR was associated with both the presence of coronary plaques >50% of the artery lumen and noncalcified coronary burden, beyond traditional cardiovascular risk factors ($P < .05$). In a noncalcified coronary burden prediction model accounting for cardiovascular risk factors, statins, and biologic treatment, MHR added value (area under the curve base model = 0.72 vs area under the curve base model plus MHR = 0.76, $P = .04$) within the American cohort. These results suggests that MHR may detect patients with psoriasis who have subclinical burden of cardiovascular disease and warrant more aggressive measures to reduce lifetime adverse cardiovascular outcomes.

Keywords: Atherosclerosis, HDL colesterol, Insulin resistance, Monocytes, Psoriasis

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INTRODUCTION

Psoriasis is a chronic immune-mediated disease associated with accelerated aterosclerosis (Gonzalez-Cantero et al, 2019). Indeed, patients with psoriasis present a higher incidence of myocardial infarction (Gelfand et al, 2006), stroke (Gelfand et al, 2009), and cardiovascular death (Dhana et al, 2019) than the general population, which reduce the life expectancy of these patients (Abuabara et al,

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Abbreviations: 18F-FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; AUC, area under the curve; CCTA, coronary computed tomography angiography; CVRF, cardiovascular risk factor; DCB, dense-calcified coronary burden; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio; NCB, noncalcified coronary burden; TB, total coronary burden

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2010). Cardiovascular risk scoring systems are a cornerstone in the prediction of adverse cardiovascular events in the general population, allowing patient stratification according to their risk and facilitating the implementation of tailored preventive strategies (Arnett et al, 2019; Visseren et al, 2021). However, because they are based on traditional cardiovascular risk factors (CVRFs), they tend to underestimate the actual risk of patients under chronic inflammatory states (Gonzalez-Cantero et al, 2022a).

Noncalcified coronary burden (NCB), which is assessed by coronary computed tomography angiography (CCTA), is an eststablished marker of early coronary atherosclerosis, associated with prospective cardiovascular events (Versteylen et al, 2013) and myocardial injury in chronic inflammatory states (Zhou et al, 2020). Furthermore, it is strongly associated with a lipid-rich prone-to-rupture coronary atherosclerosis phenotype (Lerman et al, 2017; Williams et al, 2020), being noncalcified atheroma plaques frequently identified as culprit lesions in myocardial infarction (Hoffmann et al, 2006). Both biomarkers of systemic inflammation, such as neutrophil-to-lymphocyte ratio (Dey et al, 2021), and of insulin resistance, such as triglyceride–glucose index (O'Hagan et al, 2023), have been independently associated with NCB in patients with psoriasis. Furthermore, these 2 elements, systemic inflammation and metabolic abnormalities, are closely interrelated (Hotamisligil, 2017) and may synergistically influence atherosclerosis development. In fact, inflammatory-driven changes on high-density lipoprotein (HDL) cholesterol composition have been associated with worse cardiovascular outcomes (Connelly et al, 2016; McGarrah et al, 2017).

Identifying clinical biomarkers that can effectively capture the complex inflammatory and metabolic milieu of patients with psoriasis may be needed to improve their cardiovascular risk stratification. These biomarkers should be widely available within daily clinical practice. One such parameter could be the monocyte-to-HDL ratio (MHR), which has been recently associated with higher all-cause and cardiovascular mortality in a large cohort of patients with coronary artery disease (Pei et al, 2023). In this regard, circulating monocytes have shown to predict extensive coronary plaque involvement and coronary plaque vulnerability (Lo et al, 2017; Yamamoto et al, 2018). In addition, patients with psoriasis often show decreased HDL levels compared with healthy controls (Langan et al, 2012) as well as impaired HDL function, which has been associated with higher NCB (Holzer et al, 2012; Salahuddin et al, 2015). Because HDL directly inhibits macrophage transmigration and the expression of adhesion molecules in endothelial cells (Shih et al, 2020), MHR may constitute a key parameter for capturing subclinical coronary atherosclerosis among patients under chronic inflammatory states. However, its usefulness in this context remains largely unexplored.

This study aimed to evaluate the possible association of MHR and subclinical coronary atherosclerosis by CCTA within 2 cohorts of patients with psoriasis (1 European and 1 American), along with its relation to systemic inflammatory and metabolic parameters previously involved in atherosclerosis development in this population.

RESULTS

European cohort

Baseline characteristics. The 110 patients of the European cohort were middle aged (48.4 ± 8.3 years), were predominately male (62%), had an elevated waist circumference (102.3 ± 15.6 cm), and had moderate-to-severe psoriasis as measured by PASI (median [interquartile interval] = 8.5 [5.5–13]). The prevalence of hypertension was 38.2%, current smoking was 40.0%, hyperlipidemia was 47.7%, type-2 diabetes was 3.6%, and metabolic syndrome was 32.7%. Thirty-seven patients (33.6%) had significant coronary stenosis as defined in Materials and Methods. Supplementary Table S1 summarizes the baseline characteristics of the European cohort.

MHR was associated with metabolic impairment, systemic inflammation, and higher prevalence of coronary subclinical atherosclerosis in patients with psoriasis. When patients were stratified into MHR terciles, patients in the third tercile were predominately males; had higher body mass index and waist circumference values; had higher prevalence of current smoking, hiperlipidemia, and metabolic syndrome; and had elevated high-sensitivity CRP (hs-CRP) levels. As expected, HDL and apolipoprotein A1 levels were lower than 1° and 2° terciles. Remarkably, the prevalence of significant coronary stenosis increased as MHR levels increased, so that it was 22% in the first tercile, 30% in the second tercile, and 49% in the third tercile ($P < .05$) (Table 1).

MHR was found to be positively correlated with central obesity (waist circumference, rho = 0.35, $P < .001$), with insulin resistance through the homeostatic model assessment of insulin resistance (HOMA-IR) (rho = 0.22, $P = .02$), and with triglyceride (rho = 0.24, $P = .01$) and hs-CRP (rho = 0.40, $P < .001$) levels. A negative correlation was found with apolipoprotein A1 (rho = −0.57, $P < .001$). Nevertheless, it did not show association with PASI score (rho = −0.01, $P = .89$).

We further explored the relationship between MHR and subclinical coronary atherosclerosis in univariable and multivariable logistic regression models. MHR was associated with significant coronary stenosis in unadjusted (OR = 1.13, 95% confidence interval = 1.04–1.23) and fully adjusted (OR = 1.14, 95% confidence interval = 1.02–1.27) models (Table 2).

However, receiver operating characteristic curve (ROC) analysis did not show that MHR added incremental value to base model in predicting significant coronary stenosis (area under the curve [AUC] for base model = 0.79 vs AUC for MHR model = 0.80, $P = .76$), neither did HDL (AUC for base model = 0.79 vs AUC for HDL model = 0.79, $P = .84$) nor monocyte counts (AUC for base model = 0.79 vs AUC for monocyte model = 0.79, $P = .87$).

American cohort

Baseline characteristics. The 295 patients of the American cohort were middle aged (49.7 ± 12.8 years), were predominately male (62%) and Caucasians (78.6%), and had elevated waist-to-hip ratio (median [interquartile interval] = 1.0 [0.9–1.0]). The prevalence of hyperlipidemia was 35.6%,

Table 1. Clinical Characteristics, Blood Variables and Coronary Variables of Patients with Psoriasis from the European Cohort Stratified by MHR Terciles

	MHR < 9.18	MHR = 9.18–13.65	MHR > 13.65	
Demographics and Clinical Characteristics	**n = 36**	**n = 37**	**n = 37**	***P*-Value**
Age, y	49.2 (7.9)	49.5 (7.8)	46.4 (8.9)	.20
Males, n (%)	20 (56)	26 (70)	33 (89)	**.006, .002**[1]
BMI, kg/m^2	27.0 (25.0–29.3)	29.0 (24.7–31.9)	30.3 (25.8–34.9)	**.036**
Waist circumference, cm	97.0 (12.0)	101.9 (17.1)	108.9 (15.6)	**.012**
Hypertension, n (%)	11 (31)	16 (43)	15 (41)	.50, .39[1]
Current smoker, n (%)	9 (25)	14 (38)	21 (57)	**.020, .006**[1]
Hyperlipidemia, n (%)	12 (33)	17 (47)	23 (62)	**.048, .014**[1]
Diabetes mellitus, n (%)	0 (0)	2 (5)	4 (11)	.13, **.042**[1]
Metabolic syndrome, n (%)	5 (14)	13 (35)	18 (49)	**.006, .002**[1]
Statin use, n (%)	6 (17)	6 (16)	13 (35)	.087, .060[1]
hs-CRP, mg/l	1.3 (.7–2.4)	2.6 (1.57–4.8)	2.6 (1.5–7.1)	**.002**
Monocytes/mm^3, abs	380 (345–430)	500 (450–570)	680 (600–840)	**<.001**
Cholesterol, mg/dl	211 (191–228)	203 (180–231)	198 (170–216)	.19
LDL cholesterol, mg/dl	134 (110.5–144.5)	126 (110–147)	126 (105–148)	.87
HDL cholesterol, mg/dl	57 (49–66.5)	47 (42–52)	40 (37–47)	**<.001**
Apolipoprotein A1, mg/dl	172 (157–195)	157 (139–163)	137 (130–149.5)	**<.001**
Apolipoprotein B, mg/dl	101 (86–111)	108 (92–127)	108 (99.5–125)	.31
Triglycerides, mg/dl	90.5 (62–139)	107 (79–138)	118 (82–152)	.17
Insulin	7.8 (6.05–10.15)	9.15 (6.35–12.3)	8.7 (6.9–17.3)	.27
HOMA-IR	1.71 (1.35–2.31)	2.15 (1.31–2.84)	1.82 (1.35–4.37)	.31
PASI score	8 (5.5–12.5)	8.75 (5.95–14)	8 (4.5–13)	.62
Coronary stenosis, n (%)	8 (22)	11 (30)	18 (49)	**.048, .017**[1]

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment for insulin resistance; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio.

Values reported in the table as mean ± SD for parametric variables or median (interquartile interval) for nonparametric ones. ANOVA test was used for parametric variables, and Kruskal–Wallis test was used for nonparametric ones. Pearson's chi-square test and chi-square test for trend were used for categorical variables. *P*-values ≤.05 are significant and are indicated in bold.

[1]Chi-square test for trend.

hypertension was 27.5%, current smoking was 10.5%, type-2 diabetes was 10.5%, and metabolic syndrome was 30.5%. Psoriasis severity was mild to moderate (PASI, median [interquartile interval] = 6.0 [3–10.3]), with 90 patients (30.5%) on biologic treatment. Supplementary Table S2 summarizes the baseline characteristics of the American cohort.

MHR was associated with worse cardiometabolic profile and higher systemic inflammatory burden in patients with psoriasis. After stratification into terciles by MHR, patients in the higher MHR tercile had a higher body mass index and waist-to-hip ratio; higher prevalence of hypertension and metabolic syndrome; higher levels of total cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, insulin, and insulin resistance through HOMA-IR; and higher hs-CRP than those with lower MHR levels ($P < .05$). Conversely, apolipoprotein A1 was higher in lower MHR terciles (Table 3).

MHR was positively correlated with the following markers of systemic inflammation and metabolic disarrangement: central obesity (waist-to-hip ratio, rho = 0.34, $P < .001$), HOMA-IR (rho = 0.40, $P < .001$), triglycerides (rho = 0.35, $P < .001$), hs-CRP (rho = 0.28, $P < .001$), and also with PASI score (rho = 0.13, $P = .027$); it was negatively correlated with apolipoprotein A1 (rho = −0.64, $P < .001$) and cholesterol efflux capacity (rho = −0.42, $P < .001$).

Notably, MHR appears to adequately capture systemic and organ inflammation as measured by 18^F-fluorodeoxyglucose

Table 2. Univariable and Multivariable Logistic Regression Analysis of the Association of MHR with Significant Coronary Stenosis

	Crude Model		Adjusted Model[1]	
	OR (95% CI)	***P*-Value**	**OR (95% CI)**	***P*-Value**
MHR	1.13 (1.04–1.23)	**0.005**	1.14 (1.02–1.27)	**.033**

Abbreviations: CI, confidence interval; HOMA-IR, homeostatic model of assessment for insulin resistance; MHR, monocyte-to-high-density lipoprotein ratio.

Significant coronary stenosis, dependent variable. *P*-values ≤.05 are significant and are indicated in bold.

[1]Fully adjusted for age, sex, waist circumference, hypertension, PASI, and HOMA-IR.

Table 3. Baseline Characteristics, Blood Variables, and Coronary Variables of the American Cohort according to MHR Terciles

	MHR < 7.43	MHR = 7.43–10.45	MHR > 10.45	
Demographics and Clinical Characteristics	**n = 98**	**n = 98**	**n = 99**	***P*-Value**
Age, y	50.3 ± 13.4	50.3 ± 12.2	48.6 ± 12.7	.55
Males, n (%)	40 (41)	68 (69)	75 (76)	**<.001, <.001**[1]
Ascendence, n (%)				.43
White	77 (79)	72 (73)	83 (84)	
African American	7 (7)	4 (4)	4 (4)	
Asian	8 (8)	10 (10)	6 (6)	
Unspecified	6 (6)	12 (12)	6 (6)	
Body mass index (kg/m^2)	25.3 (22.4–28.8)	29.2 (25.8–32)	31.2 (27.5–36.6)	**<.001**
Waist circumference, cm	89.4 (80–99)	98 (89–108)	106 (96–116)	**<.001**
Waist-to-hip ratio	0.92 (0.87–0.97)	0.95 (0.91–1.02)	0.99 (0.94–1.01)	**<.001**
Hypertension, n (%)	27 (28)	19 (19)	35 (35)	**.043,** .22[1]
Current smoker, n (%)	6 (6)	10 (10)	15 (15)	.12, **.034**[1]
Hyperlipidemia, n (%)	30 (31)	41 (42)	34 (34)	.25, .59[1]
Diabetes mellitus, n (%)	10 (10)	9 (9)	12 (12)	.79, .66[1]
Metabolic syndrome, n (%)	14 (14)	24 (24)	52 (53)	**<.001, <.001**[1]
Statin use, n (%)	22 (22)	25 (26)	24 (24)	.88, .77[1]
Hs-CRP, mg/l	1.1 (0.6–2.4)	1.6 (0.8–3.9)	2.7 (1.1–5.9)	**<.001**
Cholesterol, mg/dl	187.5 (161–216)	185.5 (164–211)	171 (147–197)	**.003**
LDL-cholesterol, mg/dl	95 (79–120)	110 (92–126)	101 (80–116)	**.011**
HDL-cholesterol, mg/dl	70.5 (62–86)	51 (46–58)	43 (38–48)	**<.001**
Apolipoprotein A1, mg/dl	179 (155–200)	146 (135–161)	135 (119–145)	**<.001**
Apolipoprotein B, mg/dl	83 (73–100)	93 (84–112)	93 (75–109)	**.002**
Triglycerides, mg/dl	78.5 (64–113)	107 (82–147)	122 (93–180)	**<.001**
PASI score	5.1 (2.8–9)	5.9 (3–10.8)	6.8 (3.3–11.7)	.15
Biologic treatment, n (%)	30 (31)	28 (29)	32 (32)	.85, .79[1]
Monocytes/mm^3, abs	400 (350–450)	460 (390–520)	620 (510–720)	**<.001**
Spleen (SUVmax)	3.71 (1.13)	4.03 (1.06)	5.56 (1.70)	**<.001**
Liver (SUVmax)	4.96 (1.41)	5.44 (1.45)	6.13 (2.28)	**<.001**
Bone Marrow (SUVmax)	3.96 (1.15)	4.39 (1.01)	5.27 (2.15)	**<.001**
Noncalcified coronary burden[2], mm^2	1.00 (0.40)	1.13 (0.47)	1.36 (0.54)	**<.001**
Dense-calcified coronary burden[2], mm^2	0.031 (0.011–0.096)	0.020 (0.007–0.053)	0.016 (0.005–0.047)	**.024**
Total coronary burden[2], mm^2	1.08 (0.45)	1.18 (0.49)	1.41 (0.54)	**<.001**

Abbreviations: HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio; SUVmax, maximum standardized uptake value.

Values reported in the table as mean ± SD for parametric variables or median (interquartile interval) for nonparametric ones. ANOVA test was used for parametric variables, and Kruskal–Wallis test was used for nonparametric ones. Pearson's chi-square test and chi-square test for trend were used for categorical variables. *P*-values ≤.05 are significant and are indicated in bold.

[1]Chi-square test for trend.

[2]Values provided are multiplicated ×100.

positron emission tomography/computed tomography (18^F-FDG-PET/CT) because patients in the upper terciles of MHR had higher levels of splenic, liver, and bone marrow inflammation (Table 3). Furthermore, MHR was associated with 18^F-Fluorodeoxyglucose uptake in the spleen (unadjusted: β = 0.23, $P < .001$; adjusted: β = 0.16, $P = .022$), liver (unadjusted: β = 0.25, $P < .001$; adjusted: β = 0.16, $P = .021$), and bone marrow (unadjusted: β = 0.31, $P < .001$; adjusted: β = 0.23, $P = .001$) in linear regression models (Figure 1).

Patients with higher MHR levels had higher total coronary burden and NCB. When patients grouped into MHR terciles were analyzed, those in higher terciles had higher atherosclerosis burden in terms of total coronary burden (TB) and NCB. Interestingly, those in higher terciles had lower values of dense-calcified coronary burden (DCB) (Table 3). We further explored the relationship between MHR and these markers of subclinical atherosclerosis and atherosclerosis composition in linear regression models. MHR was associated with TB in unadjusted (β = 0.31; $P < .001$) and adjusted models (β = 0.16, $P = .009$) as well as with NCB in unadjusted (β = 0.34, $P < .001$) and adjusted (β = 0.20, $P = .002$) models. No associations were found with DCB. When analyzing each of the index components separately, both monocytes and HDL were associated with TB in unadjusted but not in adjusted models. Their relationship with NCB was stronger, persisting in fully adjusted models, but with lowers β-values than MHR (Table 4).

In addition, ROC analysis showed that MHR added incremental value to the base model in predicting NCB (AUC for base model = 0.72 vs AUC for MHR model = 0.76,

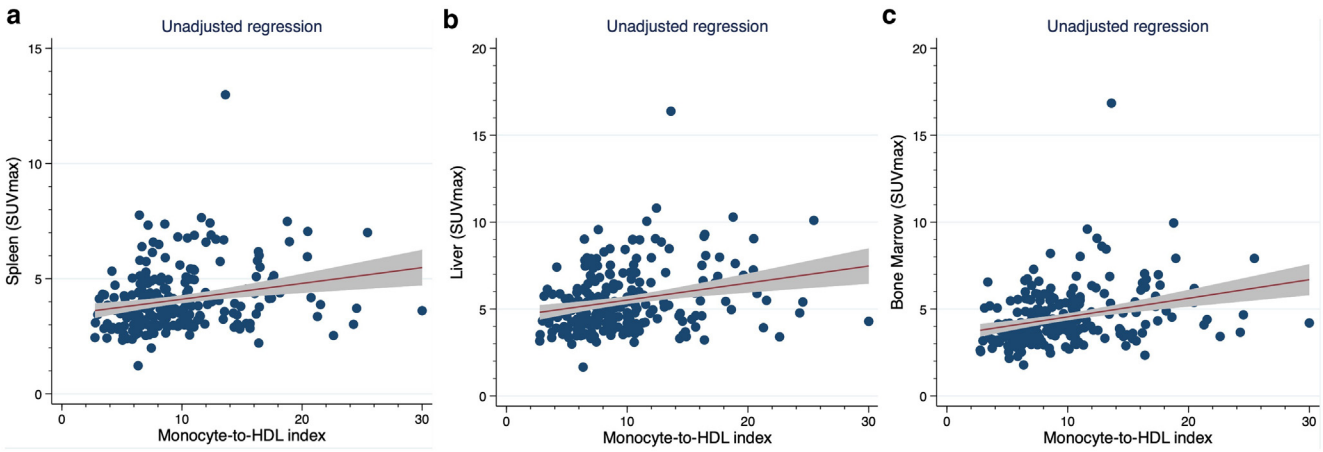

Figure 1. Linear regressions between MHR and fluorodeoxyglucose uptake in spleen, liver, and bone marrow. (**a**) Spleen SUVmax. (**b**) Liver SUVmax. (**c**) Bone marrow SUVmax. MHR, monocyte-to-high-density lipoprotein ratio; SUVmax, maximum standardized uptake value.

$P = .04$), which was not the case for HDL (AUC for base model = 0.72 vs AUC for HDL model = 0.74, $P = .14$) or monocytes (AUC for base model = 0.72 vs AUC for monocytes model = 0.74, $P = .26$) (Figure 2).

DISCUSSION

In this study including 405 patients with psoriasis from 2 international cohorts, MHR, an accessible biomarker by routine clinical practice tests, was associated with coronary subclinical atherosclerosis by CCTA independent of traditional CVRFs. Moreover, MHR seemed to adequately capture the systemic inflammatory nature of psoriasis. This was validated through the assessment of laboratory parameters, such as hs-CRP, as well as through direct examinations of inflammation in critical áreas, including the spleen, the bone marrow, and the liver using 18^{F}-FDG-PET/CT scans. In addition, MHR exhibited significant associations with the metabolic abnormalities inherent to the disease. Higher MHR terciles showed higher frequencies of metabolic syndrome and correlated with insulin resistance through HOMA-IR, among others.

Monocytes play a major role in atherosclerosis development. Circulating monocytes bind to adhesion molecules expressed in activated endothelial cells. Once in the subendothelial space, monocytes differentiate to macrophages under the stimuli of deposited oxidized LDL and inflammatory cytokines (Fuhrman et al, 2008). Local macrophages proliferate in the atheroma plaque and scavenge deposited lipids to form foam cells (Fuhrman et al, 2008; Robbins et al, 2013), both producing ROS and inflammatory molecules (Lara-Guzmán et al, 2018) involved in inflammatory propagation and plaque progression. Furthermore, macrophages produce matrix metalloproteinases capable of degrading extracellular matrix components, making plaques more vulnerable and prone to rupture (Liang et al, 2006). Indeed, high values of monocytes count at peripheral blood have been associated with severe and extensive coronary artery disease in stable patients (Lo et al, 2017) and with larger infarct sizes, impaired left ventricular ejection fraction, and microvascular occlusion in patients with ST-elevation myocardial infarction (van der Laan et al, 2012). Conversely, HDL is the critical mediator of reverse cholesterol transport, which is involved in the removal of excess

Table 4. Linear Regression Analysis between Coronary Parameters and MHR in the American Cohort

	Crude Model			Adjusted Model[1]		
Variable	Noncalcified Coronary Burden	Dense-Calcified Coronary Burden	Total Coronary Burden	Noncalcified Coronary Burden	Dense-Calcified Coronary Burden	Total Coronary Burden
MHR						
β	**0.34**	−0.07	**0.31**	**0.20**	−0.08	**0.16**
P-value	**<.0001**	.258	**<.001**	**.002**	.246	**.009**
HDL						
β	**−0.31**		**−0.27**	**−0.18**		−0.13
P-value	**<.001**		**<.001**	**.004**		.072
Monocytes						
β	**0.22**		**0.20**	**0.10**		0.08
P-value	**<.001**		**.001**	**.072**		.174

[1]Fully adjusted for age, sex, waist-to-hip ratio, hypertension, PASI, and HOMA-IR.
Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment for insulin resistance; MHR, monocyte-to-high-density lipoprotein ratio.
Crude model: Univariable linear regression. *P*-values ≤.05 are significant and are indicated in bold.

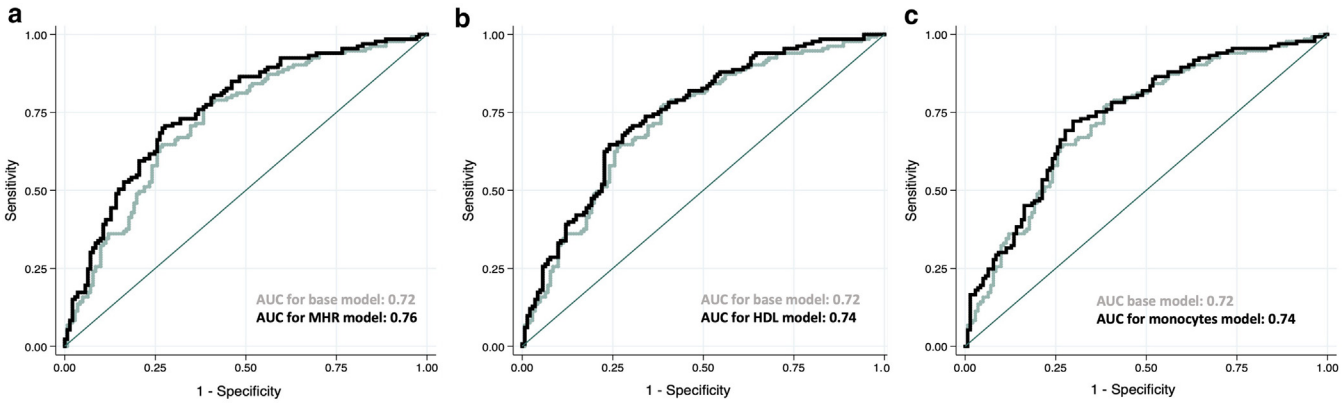

Figure 2. ROC analysis to evaluate the contribution of MHR in the identification of subjects with higher NCB. NCB was dichotomized on the basis of median. Base model was adjusted for age, sex, waist circumference, smoking status, diabetes mellitus, blood pressure, LDL cholesterol levels, statin use, and biologic treatment. MHR model, HDL model and monocytes model resulted from adding MHR, HDL, or monocytes (absolute count) to the base model, respectively. (**a**) Base model versus MHR model. (**b**) Base model versus HDL model. (**c**) Base model versus monocytes model. AUC, area under the curve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio; NCB, noncalcified coronary burden; ROC, receiver operating characteristic curve.

cholesterol from atheroma foam cells and its transport to the liver (Ono, 2012). Furthermore, HDL exerts important anti-inflammatory and antioxidative effects closely interwoven with monocyte functions (Guo and Ma, 2023). It has shown to decrease CRP- and TNFα-induced endothelial adhesion molecules (Barter et al, 2004; Keul et al, 2019) and to inhibit the expression of monocyte adhesion molecules such as CD11b (Murphy et al, 2008), hardening monocyte transmigration and activation. In addition, HDL may limit proinflammatory signaling in macrophages via toll-like receptors (De Nardo et al, 2014) and carries a number of enzymes (paraoxonase-1 and -3, among others) capable of destroying the lipid hydroperoxides that oxidize LDL (Barter et al, 2004). Collectively, these facts suggest that MHR may capture the synergistic effect that monocytes and HDL could exert on inflammatory-driven atherosclerosis development.

Nevertheless, the vast majority of studies on MHR undertaken to date included patients from the general population. In this regard, MHR has been associated with an increased all-cause and cardiovascular mortality in a study involving >34,000 participants from the National Health and Nutrition Examination Survey. Indeed, the risk of cardiovascular mortality increased by 21% per twofold change in MHR in a linear manner (Jiang et al, 2022). Furthermore, in the context of acute coronary syndromes, a recent meta-analysis has shown that MHR was independently associated with higher risk of major adverse cardiovascular events and all-cause mortality, both in the in-hospital and in the long-term follow-up subgroups (Sun et al, 2020). MHR has also been associated with contrast-induced nephropathy (Sağ et al, 2017; Ulus et al, 2018), higher thrombus burden (Arsoy et al, 2017; Sercelik and Besnili, 2018), stent thrombosis (Cetin et al, 2015), and drug-eluting stent restenosis (Nan et al, 2020) in these patients, as well as with a more complex coronary artery disease (Akboga et al, 2016; Çagdas et al, 2018) and bare-metal stent restenosis (Avc, 2019; Ucar, 2016) in patients with stable or unstable angina.

Higher NCB has been found in chronic inflammatory states (Fitch et al, 2013; Karpouzas et al, 2014), including psoriasis (Lerman et al, 2017). In this context, NCB correlated with disease activity, insulin resistance, and systemic inflammation independent of CVRFs, decreasing after 1-year biologic treatment (Dey et al, 2021; Elnabawi et al, 2019; O'Hagan et al, 2023). Thus, it likely constitutes a component of inflammatory-driven atherosclerosis. In addition, NCB has shown a strong association with a lipid-rich, prone-to-rupture atherosclerosis phenotype (Lerman et al, 2017; Williams et al, 2020) and with early myocardial injury in chronic inflammatory states (Zhou et al, 2020), probably contributing to the accelerated development of myocardial infarction in patients with psoriasis compared with that in healthy controls (Gelfand et al, 2006).

Identifying markers that capture systemic inflammation, insulin resistance, and ultimately inflammatory-driven atherosclerosis beyond traditional CVRFs could help us to fill the gap in cardiovascular risk prediction among patients with psoriasis and other chronic inflammatory conditions. In this regard, we carried out a comprehensive evaluation of MHR in a group of patients under such inflammatory states. First, it correlated with psoriasis severity (PASI score) in the American cohort. Second, it was strongly and consistently correlated with insulin resistance through HOMA-IR and with hs-CRP. Of note was its association with spleen, liver, and bone marrow inflammation on 18^{F}-FDG-PET/CT, which further reinforces its link with systemic inflammation in patients with psoriasis. Finally, MHR was independently associated with a higher prevalence of significant coronary stenosis and, remarkably, improved NCB prediction beyond monocytes and HDL when added to a predicting model already including modifiable CVRFs, statins, and biologic use. It is noteworthy that the effect estimation of MHR on subclinical atherosclerosis was remarkably reduced between crude and fully adjusted multivariable models, which adjusted for relevant CVRFs as well as insulin resistance and psoriasis severity, especially in the American cohort. It may suggest that apart from an independent effect of MHR on atherosclerosis, this biomarker could also partially mediate or capture the effect of those variables on cardiovascular disease.

Some limitations of this biomarker should be discussed. Although low HDL levels have been associated with an increased cardiovascular risk (Castelli et al, 1986; Després et al, 2000), clinical trials aimed at improving its levels failed to reduce this risk (Keene et al, 2014), and extremely high HDL values are also associated with all-cause and cardiovascular mortality (Madsen et al, 2021). This facts have shifted the attention to HDL function rather than HDL levels when exploring cardiovascular prognosis (Rohatgi et al, 2021), but the markers that would allow the evaluation of its function are still far from daily clinical practice. Cholesterol efflux capacity, which estimates HDL ability to accept cholesterol from peripheral tissues, is impaired in patients with psoriasis (Salahuddin et al, 2015) and have been inversely associated with incident cardiovascular events independent of HDL levels (Rohatgi et al, 2014). HDL anti-inflammatory capacity, referred to as the ability to suppress TNFα-induced endothelial adhesion molecules, was also inversely associated with incident cardiovascular events independent of cholesterol efflux capacity (Jia et al, 2021). Because HDL function is impaired by systemic inflammation (Connelly et al, 2016; McGarrah et al, 2017; Rohatgi et al, 2021), and MHR seems to adequately capture it, it is likely that the index may partially reflect these functional disarrangements. Indeed, MHR correlated with cholesterol efflux capacity and with apolipoprotein AI in our study, which not only facilitates cholesterol efflux but also exhibits intrinsic antioxidant and anti-inflammatory attributes (Barter et al, 2004).

Other limitations of the study include its cross-sectional design, which may introduce some bias and prevent us from determining directionality of high MHR in atherosclerosis progression. We have also not explored how extreme HDL levels affect the index because the rarity of this trait requires a sample size that exceeds that available in the study. Coronary outcomes were different between the 2 cohorts because they were independently designed and therefore collected different coronary variables. Nevertheless, it enabled us to conduct a more in-depth exploration of the association between MHR and coronary atherosclerosis, evaluating its association with a clinically significant indicator of established atherosclerosis (stenosis $\geq$ 50%) and with the composition of coronary plaques, especially with those components more involved in inflammatory-driven atherosclerosis (NCB). Finally, MHR values for grouping patients into terciles were slightly different between the 2 cohorts, which may reflect a different systemic inflammatory burden among them. Our study constitutes a first approach for evaluating how higher levels of MHR associate with different atherosclerosis-related markers in patient with psoriasis. That categorization should be understood as a method to visualize those differences and not as an attempt to identify cutoff values. Further studies on larger cohorts and aimed at establishing such MHR cutoffs among different populations will be needed in the coming years.

In conclusion, in this study, MHR was independently associated with higher coronary subclinical atherosclerosis in patients with psoriasis, a finding validated in 2 international cohorts. It consistently correlated with insulin resistance and systemic inflammatory parameters, which are not adequately captured by cardiovascular risk scoring systems. Collectively, our findings suggest that MHR, a widely accessible biomarker within daily clinical practice, may help in identifying a subset of patients with psoriasis with higher subclinical burden of cardiovascular disease and therefore warranting more aggressive measures to reduce their lifetime adverse cardiovascular outcomes. Further research is needed to confirm these findings in larger cohorts of patients and to assess MHR value in incident cardiovascular disease in patients with chronic inflammation.

MATERIALS AND METHODS

A total of 405 patients with psoriasis were included in a cross-sectional study: 110 participants from the European cohort and 295 participants from the American cohort. Study protocols were approved by the institutional review boards of the Hospital Ramón y Cajal (Madrid, Spain) and of the National Institutes of Health (Bethesda, MD) for the European and the American cohort, respectively. Participants provided written informed consent before study enrolment. The study followed the relevant portions of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (von Elm et al, 2008).

European cohort

Study population. A total of 110 patients with psoriasis were consecutively recruited from January 2020 to May 2023 at the Department of Dermatology of the Hospital Ramón y Cajal. Patients were included in the Early Detection of Subclinical Atherosclerosis in Psoriasis (EDSAP) cohort (Abbad-Jaime De Aragón et al, 2023). This is an ongoing observational, longitudinal, and prospective cohort study that includes patients aged 30–65 years, diagnosed with moderate-to-severe psoriasis (PASI >10 or body surface area >10%) clinically by an expert physician, and deemed suitable for starting biologic therapy by the investigator. These patients were also biologic therapy naïve or had discontinued such therapy within the previous 3 months. Exclusion criteria were as follows: history of cardiovascular disease, active infection within the past 72 hours, the presence of any comorbid condition known to promote cardiovascular disease or systemic inflammation different from traditional CVRFs, current oncological treatment, history of transplantation with active immunomodulatory treatment, morbid obesity, and chronic liver or kidney disease. Data from the baseline visit were used for this study. The recruitment is detailed in Supplementary Figure S1.

Clinical evaluation and biochemical measurements. Through clinical interview and physical examination, the investigators collected demographic data; data on severity of psoriasis measured with PASI; data on the presence of other comorbid conditions; and blood pressure, height, weight, and waist circumference data for each participant. Fasting blood samples were collected and analyzed for basic chemistry, blood count, hs-CRP, complete lipid profile, and insulin. MHR was calculated as the ratio of absolute monocyte count/mm^3 to HDL in mg/dL. Metabolic syndrome was defined according to the harmonized International Diabetes Federation criteria (Alberti et al, 2006). Arterial hypertension was defined by a systolic blood pressure $\geq$140 mmHg, a diastolic blood pressure $\geq$90, a documented history of hypertension, or self-reported use of antihypertensive medication. Hyperlipidemia was defined by total cholesterol $\geq$240 mg/dl, LDL cholesterol $\geq$160 mg/dl, HDL cholesterol $\geq$40 mg/dl, a documented history of hyperlipidemia, or

self-reported use of lipid-lowering drugs. Diabetes was defined by fasting plasma glucose ≥126 mg/dl, a documented history of diabetes, or self-reported treatment with hypoglycemic medication. Patients actively smoking at the time of inclusion were considered current smokers.

Coronary subclinical atherosclerosis assessment. The presence of coronary atherosclerosis was assessed using a CCTA scan. CCTA is performed with a 320-detector CT scanner (Aquilion ONE VISION, Toshiba), following the guidelines of the National Institutes of Health Radiation Exposure Committee. Scans were performed with prospective or retrospective electrocardiogram gating according to heart rate, tube potential of 100 or 120 kV, and tube current of 100−850 mA adjusted to the patient's body size, with a gantry rotation time of 275 ms. Images were acquired with a slice thickness of 0.5 mm and a slice increment of 0.25 mm.

American cohort

Study population. The Psoriasis Atherosclerosis and Cardiometabolic Disease Initiative (PACI) enrolled 378 consecutive participants with psoriasis from January 2013 to February 2022 (NCT01778569). The detailed inclusion and exclusion criteria of the study have been previously described (Harrington et al, 2017). Of them, 295 had quantifiable CCTA scans and plasma values including monocytes available at baseline. Recruitment is detailed in Supplementary Figure S2.

Clinical evaluation and biochemical measurements. Participant demographics; clinical history; and physical examination, including anthropometric measurements, were obtained at the time of recruitment. Psoriasis skin burden was evaluated with PASI score. Participants also reported the medication they were on at recruitment, including biologic therapy (anti-TNFα, anti−IL-12/23, anti−IL-17) and statins. Overnight fasting blood samples were collected and analyzed for basic chemistry, fasting glucose, lipid panel, insulin, blood count, and inflammatory markers. MHR, metabolic syndrome, arterial hypertension, hyperlipidemia, diabetes mellitus, and current smoking were defined analogously to the European cohort.

Spleen, liver, and bone marrow inflammation measured by 18^F-FDG-PET/CT. The 18^F-FDG-PET/CT imaging was obtained using one Siemens Biograph mCT PET/CT 64-slice scanner (Siemens Medical Solutions) after an overnight fast for a minimum of 8 hours. All patients underwent the same positron emission tomography/computed tomography protocol as previously described (Teague et al, 2023). Bone marrow, liver, and splenic uptakes were measured using positron emission tomography/computed tomography image analysis program (OsirixTM, version 5.8.5, Pixmeo SARL). Bone marrow uptake was quantified by placing volumetric regions of interests over axial and sagittal sections within individual vertebrae from T1 to L5, recording the average maximum standardized uptake value of the 17 individual vertebrae. Splenic uptake was measured by placing a single volumetric region of interest with 8.0 cm^3 volume within the splenic margin, and a single maximum standardized uptake value was acquired. Liver uptake was measured by placing a spherical 9 cm^3 region of interest within the hepatic margin.

Coronary atherosclerosis burden characterization. All participants underwent CCTA in the same scanner (320-detector row Aquilion ONE ViSION, Toshiba) as previously reported (Gonzalez-Cantero et al, 2022b). NCB was assessed separately in each of the main coronary arteries >2 mm in diameter (left anterior descending, left circumflex, and right coronary artery) using QAngio CT (Medis Medical Imaging). NCB, DCB, and TB were calculated by dividing total vessel plaque volume by total vessel length to account for variable coronary artery lengths and subsequently adjusting for mean luminal intensity to yield TB, DCB, and NCB using adaptive threshold for cutoff values (Shin et al, 2021).

Study outcome

In both cohorts, the primary outcome was subclinical atherosclerosis. In the European cohort, the outcome was the presence of a significant coronary stenosis, defined as a lesion causing ≥50% of lumen narrowing of any coronary artery (Neumann et al, 2019). In the American cohort, it was the amount of TB, NCB, and DCB.

Statistical analysis

Values are reported as mean (SD) for parametric variables, median (interquartile interval) for nonparametric variables, and n (%) for categorical variables. Normality was evaluated using skewness, kurtosis, and histogram plots. Statistical significance was assessed by Student's *t*-test when comparing 2 groups and ANOVA test in multiple groups comparison for parametric variables; Wilcoxon rank-sum test and Kruskal−Wallis test were applied for nonparametric ones. Pearson's chi-square test was used for categorical variables. Patients were stratified into MHR terciles because it facilitated better grouping based on visual differences in box-and-whisker plots for clinical, analytical, and coronary variables. Because terciles were an ordinal variable, in addition to the chi-square test, chi-square test for trend was conducted to evaluate the association of terciles with binary variables and assess whether binary variables percentages present an increasing linear trend as terciles increase. Spearman's correlations were also applied to evaluate the relationship of MHR with cardiometabolic and inflammatory quantitative markers in both cohorts. Multiplicity was not addressed given the exploratory nature of the study and given that the association of MHR with the primary outcome was fully adjusted in multivariable models. Analyses were performed with StataIC 17 (Stata, College Station, TX). $P \leq .05$ was considered statistically significant.

Multivariable analysis. Multivariable regressions models were conducted to further explore the usefulness of MHR as a biomarker of coronary subclinical atherosclerosis, in the sense that it captures risk independent of recognized factors that influence subclinical atherosclerosis in psoriasis: multivariable logistic regression in the European cohort (significant coronary stenosis as outcome, ORs were reported) and multivariable linear regression in the American cohort (NCB, DCB, and TB as outcomes, standardized betas were reported). The initial maximum model included potential confounders that have been previously related to both metabolic abnormalities/systemic inflammation and subclinical atherosclerosis (age, sex, hypertension, current smoking status, LDL, diabetes mellitus, body mass index, waist circumference, waist-to-hip ratio, HOMA-IR, hs-CRP, and PASI score), whose hypothetical causal relationships with MHR and study outcomes are depicted in Figure 3. Statin therapy and biologic treatment, as potential modifiers of previous variables, were also considered as potential confounders (the latter only in the American cohort). First-order interactions among confounders and exposure (MHR) were evaluated. Collinearity was assessed through variance inflation factor. After excluding collinear variables with less clinical significance and nonsignificant interactions, the final model accounted for those confounders

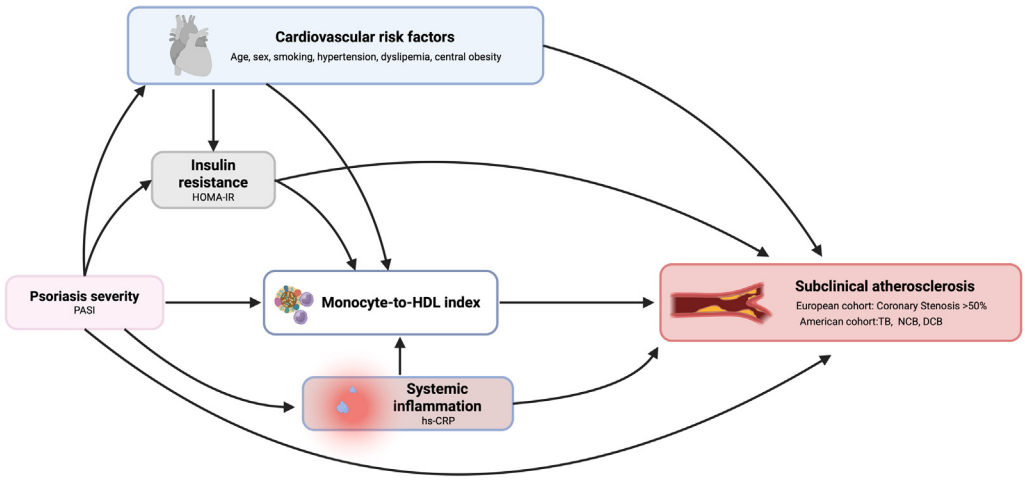

Figure 3. Directed acyclic graph representing the hypothetical relationships between confounders of the association of MHR with subclinical atherosclerosis. DCB, dense-calcified coronary burden; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity CRP; MHR, monocyte-to-high-density lipoprotein ratio; NCB, noncalcified coronary burden; TB, total coronary burden.

relevant for adjustment (those that modify at least 10% of the MHR effect on outcome) to attain model's parsimony while ensuring the most precise estimation (with the lowest standard error) of the MHR effect (Doménech and Navarro, 2023).

ROC analyses. ROC analyses were carried out to quantify the contribution of MHR in identifying subjects with significant coronary subclinical atherosclerosis (European cohort) and higher NCB (American cohort), for which NCB was dichotomized on the basis of median. Multivariate logistic regressions were then conducted in both cohorts to compare the AUC between the base model and the base model plus MHR (MHR model), plus HDL (HDL model), and plus monocytes (monocytes models) to explore whether MHR added more value than each component separately. The base model was adjusted for age, sex, waist circumference, smoking status, diabetes mellitus, blood pressure, LDL cholesterol levels, and statin use, factors usually employed for cardiovascular risk prediction and modification in clinical practice. The base model for the American cohort was further adjusted for biologic treatment because it has shown to reduce NCB over a year (Elnabawi et al, 2019).

DATA AVAILABILITY STATEMENT

We do not publicly post our data; we would be happy to supply them to any investigator with a reasonable request. This is the policy at our institution.

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CONFLICT OF INTEREST

ML-V has potential conflict of interests (advisory board member, consultant, research support, participation in clinical trials, and honorary for speaking) with the following pharmaceutical companies: Abbvie, Amirall, Amgen, Bristol, Boehringer, Cellgene, Janssen-Cilag, Kyowa-kirin, Leo Pharma, Novartis, Lilly, and UCB. JMG served as a consultant for Abbvie, Artax (DSMB), BMS, Boehringer Ingelheim, Celldex (DSMB), FIDE (which is sponsored by multiple pharmaceutical companies), GSK, Inmagene (DSMB), Twill, Lilly (DMC), Leo, Moonlake (DSMB), Janssen Biologics, Novartis, UCB (DSMB), Neuroderm (DSMB), and Veolia North America, receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from Amgen, BMS, and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by pharmaceutical sponsors. JMG is a copatent holder of resiquimod for treatment of cutaneous T-cell lymphoma. JMG is a Deputy Editor for the *Journal of Investigative Dermatology*, receiving honoraria from the Society for Investigative Dermatology; is Chief Medical Editor for Healio Dermatology (receiving honoraria); and is a member of the Board of Directors for the International Psoriasis Council and the Medical Dermatology Society, receiving no honoraria. NNM is a full-time United States government employee and has served as a consultant for several pharmaceutical companies, receiving grants and/or research funding, and as a principal investigator for the National Institutes of Health, receiving grants and/or research funding. AG-C has served as a consultant for Abbie, Janssen, Novartis, Lilly, Almirall, Celgene, and Leo Pharma, receiving grants/other payments. The remaining author state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: EB-R, NNM, AG-C; Data Curation: EB-R, CA-JdA, AB-M, JP-B, JS, LF-F, PJ-O, CA-L, EG-M, BdN-R; Formal Analysis: EB-R, CA-JdA, AG-C; Funding Acquisition: NNM, AG-C; Investigation: EB-R, CA-JdA, JP-B, AB-M, NNM, AG-C; Methodology: EB-R, NNM, AG-C; Project Administration:

EB-R, NNM, AG-C; Resources: EB-R, JS, LF-F, ML-V, MC-G, MGB, PJ-O, NNM, AG-C; Software: EB-R, JS, LF-F, NNM, AG-C; Supervision: EB-R, LF-F, MGB, PJ-O, JMG, NNM, AG-C; Validation: EB-R, LF-F, MGB, JMG, NNM, AG-C; Visualization: EB-R, JMG, NNM, AG-C; Writing − Original Draft Preparation: EB-R, CA-JdA, AB-M, JP-B, JS, LF-F, ML-V, MGB, CA-L, EG-M, BdN-R, JNR, NNM, AG-C; Writing − Review and Editing: EB-R, CA-JdA, AB-M, JP-B, JS, LF-F, ML-V, MC-G, MGB, JNR, PJ-O, JMG, NNM, AG-C

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2024.02.015.

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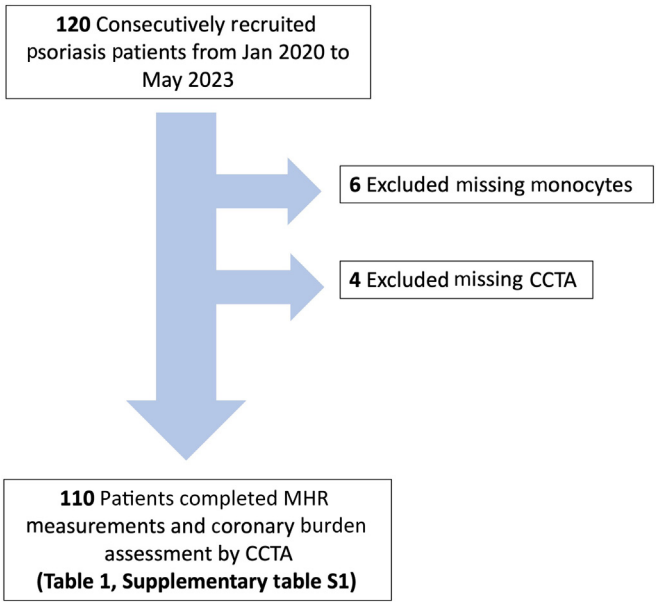
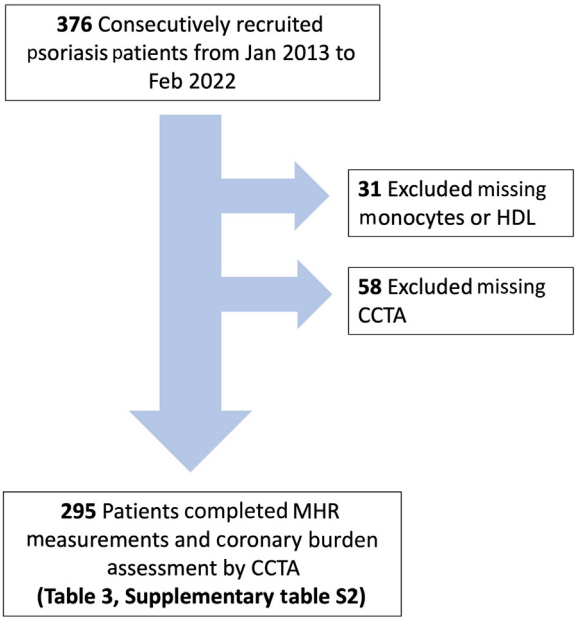


Supplementary Figure S1. CONSORT diagram. CCTA, coronary computed tomography angiography; CONSORT, Consolidated Standards of Reporting Trials; Jan, January; MHR, monocyte-to-high-density lipoprotein ratio.



Supplementary Figure S2. CONSORT diagram. CCTA, coronary computed tomography angiography; CONSORT, Consolidated Standards of Reporting Trials; HDL, high-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio.

Supplementary Table S1. Baseline Characteristic of the European Cohort

Baseline Characteristic	n = 110
Demographics and clinical characteristics	
Age, y	48.4 (8.3)
Males, n (%)	79 (71.8)
BMI (kg/m^2)	28.12 (25.15–32.10)
Waist circumference, cm	102.29 (15.56)
Hypertension, n (%)	42 (38.2)
Current smoker, n (%)	44 (40.0)
Hyperlipidemia, n (%)	52 (47.7)
Type-2 diabetes, n (%)	4 (3.6)
Metabolic syndrome, n (%)	36 (32.7)
Statin use, n (%)	25 (22.7)
Metabolic and inflammatory characterization	
hs-CRP, mg/l	2.1 (1.3–4.8)
Monocytes, abs	525 (410–630)
Total colesterol, mg/dl	203.6 (34.20)
LDL cholesterol, mg/dl	130.2 (30.4)
HDL cholesterol, mg/dl	47 (41–56)
Apolipoprotein A1 cholesterol, mg/dl	155 (134–171)
Apolipoprotein B cholesterol, mg/dl	107.0 (20.8)
Triglycerides, mg/dl	106.5 (72–139)
Insulin	8.5 (6.3–11.8)
HOMA-IR	1.86 (1.35–2.64)
Monocyte-to-HDL ratio	10.7 (8.4–15.1)
Psoriasis characterization	
PASI score	8 (5.5–13)
Coronary characterization	
Significant coronary stenosis, n (%)	37 (33.6)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment for insulin resistance; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein.

Values are reported in the table as mean ± SD for parametric variables or median (interquartile interval) for nonparametric ones.

Supplementary Table S2. Baseline Characteristics of the American Cohort

Baseline Characteristics	n = 295
Demographics and clinical characteristics	
Age, y	49.72 (12.79)
Males, n (%)	183 (62.0)
Ascendence, n (%)	
White	232 (78.6)
African American	15 (5.1)
Asian	24 (8.1)
Unspecified and others	24 (8.1)
BMI (kg/m^2)	28.75 (24.9–32.5)
Waist-to-hip ratio	0.95 (0.90–1)
Hypertension, n (%)	81 (27.5)
Current smoker, n (%)	31 (10.5)
Hyperlipidemia, n (%)	105 (35.6)
Type-2 diabetes, n (%)	31 (10.5)
Metabolic syndrome, n (%)	90 (30.5)
Statin use, n (%)	71 (24.1)
Metabolic and inflammatory characterization	
hs-CRP, mg/l	1.7 (0.8–4)
Monocytes, abs	470 (400–570)
Total cholesterol, mg/dl	183 (157–208)
LDL cholesterol, mg/dl	103.5 (84–122)
HDL cholesterol, mg/dl	52 (44–65)
Apolipoprotein A1 cholesterol, mg/dl	148 (134–169)
Apolipoprotein B cholesterol, mg/dl	91 (76–107)
Triglycerides, mg/dl	101 (72–147)
Insulin	11 (6.9–18.4)
HOMA-IR	2.75 (1.58–4.60)
Monocyte-to-HDL ratio	8.84 (6.67–11.52)
Psoriasis characterization	
PASI score	6 (3–10.3)
Biologic treatment, n (%)	90 (30.5)
Coronary characterization[1]	
Noncalcified coronary burden, mm^2	1.16 (0.49)
Dense-calcified coronary burden, mm^2	0.02 (0.007–0.054)
Total coronary burden, mm^2	1.22 (0.51)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment for insulin resistance; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein.

Values are reported in the table as mean ± SD for parametric variables or median (interquartile interval) for nonparametric ones.

[1]Values provided are multiplicated ×100.