Metabolic Syndrome Diagnosis Changes and Psoriasis Risk: A Nationwide Population-Based Study

Hyun Ji Lee
The Catholic University of Korea
Kyung Do Han
Soongsil University
Hae Eun Park
The Catholic University of Korea
Ju Hee Han
The Catholic University of Korea
Chul Hwan Bang
The Catholic University of Korea
Young Min Park
The Catholic University of Korea
Ji Hyun Lee (ejee@catholic.ac.kr)
The Catholic University of Korea

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Abstract

Background

Metabolic syndrome (MetS) is associated with psoriasis, but it remains unclear whether the risk of psoriasis remains in patients whose MetS diagnosis changes.

Objectives

To assess the associations between psoriasis risk and changes in MetS components.

Methods

We obtained data from the National Health Insurance Service of Korea and divided the participants into four groups: individuals without MetS (control); individuals with MetS in 2009 but without it in 2012 (pre-MetS); individuals without MetS in 2009, but with newly diagnosed MetS in 2012 (post-MetS); and individuals with MetS during the 2009–2012 period (continuous-MetS). We calculated the risk of psoriasis for each group.

Results

Psoriasis risks were similar in the control and pre-MetS groups, but were significantly higher in the post-MetS group (hazard ratio [HR], 1.08495%; 95% confidence interval [CI], 1.045–1.124) and in the continuous-MetS group (HR, 1.106; 95% CI, 1.068–1.145) than in the control group. Among MetS components, waist circumference showed the strongest association with psoriasis, followed by high-density lipoprotein and triglyceride levels.

Conclusion

Psoriasis risk was higher in patients with sustained or newly developed MetS than in those who did not have MetS (regardless of prior MetS status).

1. Introduction

Psoriasis is a chronic, immune-mediated skin disease that affects an estimated 125 million people worldwide[1]. The pathophysiology of psoriasis involves a variety of inflammatory cells that secrete cytokines, thereby stimulating the activity of myeloid dendritic cells. The predominant feature involves IL-23-mediated activation of the Th17 pathway[2]. Genetic factors play an important role in the development of psoriasis, and environmental factors can exacerbate the disease. Psoriasis is a disease of the skin and

joints, as well as a systemic inflammatory process associated with a range of comorbidities[3]. Metabolic syndrome (MetS), which includes hyperglycemia, atherogenic dyslipidemia, elevated blood pressure, and abdominal obesity[4,5], increases the risks of cardiovascular disease and all-cause mortality[6].

During the past two decades, studies concerning the association between MetS and psoriasis have been actively conducted[7]. In one nationwide population-based study, MetS was positively associated with an increased rate of psoriasis, and this trend became more pronounced in individuals with more MetS components[8]. Furthermore, a prospective study showed that MetS (especially its obesity component) was associated with an increased risk of incident psoriasis[9]. Many studies concerning the association between the two diseases exist, but none have investigated whether the risk of psoriasis is affected by changes in the MetS diagnosis.

Here, we assessed the associations between psoriasis risk and changes in MetS components using data from the Korean National Health Insurance Service (KNHIS) database.

2. Materials And Methods

2.1. Data Source

We extracted data from the National Health Claims database of the KNHIS[10]. This database represents the entire Korean population, and maintains data comprising inpatient and outpatient medical service records, diagnostic and procedural codes, prescribed medication claims, and patient demographics. All Korean nationals receive a unique identification number at birth; accordingly, their health care records cannot be duplicated or omitted. The KNHIS uses the standard codes of the International Statistical Classification of Diseases and Related Health Conditions, 10th revision (ICD-10). The KNHIS also provides general health check-ups and a cancer-screening program. Therefore, all insured Koreans and their dependents enjoy free age-relevant health checkups. We ensured that the data extracted from the KNHIS were complete and anonymized, and the Institutional Review Board of the KNHIS approved our request for these data (NHIS-2019-1-075). In addition, the Ethics Committee of Seoul St. Mary's Hospital, at the Catholic University of Korea, approved our study design and waived the requirement for informed consent from the participants (KC18ZESI0639).

2.2. Study Design and Population

We included data from 5,644,324 adults who underwent health examinations including measurement of MetS components in 2009 and in 2012. We used the following definition of MetS in this study (in accordance with the revised criteria of the National Cholesterol Education Program Adult Treatment Panel III)[11]: MetS is present in any individual with three or more of the five MetS components (waist circumference ≥ 90 cm for men and ≥ 85 cm for women, in accordance with the Korean Society for the Study of Obesity cut-off point for abdominal obesity [12]; triglyceride [TG] levels ≥ 150 mg/dL or the use of medication for elevated TG; high-density lipoprotein [HDL] cholesterol levels < 40 mg/dL for men and < 50

mg/dL for women or the use of medication to reduce LDL-cholesterol; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or the use of antihypertensive medication; fasting glucose levels ≥ 100 mg/dL or the use of medication for elevated glucose levels). We divided the participants into four groups: individuals without MetS in both 2009 and 2012 (control); individuals with MetS in 2009, but not in 2012 (pre-MetS); individuals without MetS in 2009, but with new onset diagnosis in 2012 (post-MetS); and individuals with MetS during the 2009–2012 period (continuous-MetS). We assessed the associations between MetS components (waist circumference, blood pressure, fasting glucose, and TG and HDL levels) and psoriasis for each group. We tracked the data for all study participants (their health care records) during the 6-year period from 2012 to 2017 to identify patients who developed psoriasis (ICD-10: L40).

2.3. Clinical, Laboratory, and Anthropometric Measurements

The KNHIS regular medical heath examination program includes information concerning variables that may alter the general health status. The following data were obtained in this study: sex, age, smoking and alcohol consumption statuses, and physical activity level. Detailed smoking status, alcohol consumption, and physical activity histories (including the amounts and frequencies) were obtained from checkup program questionnaires. We classified individuals as nonsmokers, ex-smokers, and current smokers based on their smoking status. We defined alcohol consumption habits into three categories: abstinence (no alcoholic drinks consumed within the past year), moderate drinking (< 30 g pure alcohol per day), and heavy drinking (≥ 30 g pure alcohol per day). We classified individuals' physical activity habits as vigorous-moderate or absent. Vigorous-moderate physical activity was defined as ≥ 1 day per week of moderate or vigorous intensity exercise. Venous blood samples for the measurement of fasting glucose, lipid profiles, and liver enzyme levels were obtained at each examination site after an overnight fast. Body mass indexes (BMIs) were calculated based on each participant's weight (in kilograms) divided by the square of their height (in meters); these measurements were taken during the checkup programs. The checkup programs also included measurements of systolic and diastolic blood pressures, and of waist circumference[13].

2.4. Statistical Analysis

For the study population characteristics in the four groups, we analyzed continuous variables using the independent *t*-test and dichotomous variables using the χ^2 test. We analyzed variables with skewed distributions after logarithmic transformation. The data are shown as means ± standard deviations (continuous variables), numbers and percentages (dichotomous variables), or geometric means and 95% confidence intervals (CIs) (continuous variables with skewed distributions). We performed univariate and multivariate Cox proportional hazard regression analyses to evaluate the associations of MetS component changes with psoriasis risk. We also performed a multivariate Cox proportional hazard regression analysis adjusting for age, sex, smoking status, alcohol consumption, physical activity, and BMI. We used log-rank tests to analyze the hazard ratios (HRs) for psoriasis for each group. All statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA). *P* values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

We compared the results of health examinations in 2009 and 2012 among the four groups (control group, n = 3,439,976; pre-MetS group, n = 430,044; post-MetS group, n = 752,360, and continuous-MetS group, n = 1021944). Table 1 shows total patient demographics by group.

Table 1
Characteristics of the study population

Group	Control	Pre-MetS	Post-MetS	Continuous-MetS	*p*
Number	3439976	430044	752360	1021944	
Age (year)	46.91 ± 12.28	54.22 ± 12.62	53.41 ± 12.63	58.86 ± 12.04	< 0.0001
20–39 (%)	1051997 (30.58)	57713 (13.42)	117586 (15.63)	70411 (6.89)	
40–64 (%)	2073796 (60.29)	277203 (64.46)	484489 (64.4)	603283 (59.03)	
≥ 65 (%)	314183 (9.13)	95128 (22.12)	150285 (19.98)	348250 (34.08)	
Sex (Masculine) (%)	1994779 (57.99)	273870 (63.68)	458596 (60.95)	549278 (53.75)	< 0.0001
Smoking					< 0.0001
Non-smoker (%)	2005130 (58.32)	229903 (53.48)	410512 (54.58)	613413 (60.04)	
Ex-smoker (%)	594935 (17.3)	89452 (20.81)	151765 (20.18)	197190 (19.3)	
Current smoker (%)	838113 (24.38)	110492 (25.7)	189846 (25.24)	211010 (20.65)	
Alcohol consumption					< 0.0001
Abstinence (%)	1634380(47.59)	217310 (50.59)	381161 (50.73)	601862 (58.96)	
Moderate (%)	1610960 (46.91)	181200 (42.19)	313829 (41.77)	350634 (34.35)	
Heavy (%)	188808 (5.5)	31001 (7.22)	56415 (7.51)	68277 (6.69)	
Physical activity (vigorous-moderate) (%)	2088458 (60.75)	250249 (58.23)	424278 (56.42)	533465 (52.23)	< 0.0001
Household income (low) (%)	666885 (19.39)	92797 (21.58)	164967 (21.93)	236763 (23.17)	< 0.0001
Place (urban) (%)	1531175 (44.51)	184593 (42.92)	325629 (43.28)	442651 (43.31)	< 0.0001

Group	Control	Pre-MetS	Post-MetS	Continuous-MetS	*p*
Height (cm)	165.08 ± 8.91	164.28 ± 9.62	164.11 ± 9.65	162.21 ± 9.9	< 0.0001
Weight (kg)	62.69 ± 10.77	66.89 ± 11.8	68.39 ± 12.42	69.12 ± 12.89	< 0.0001
Systolic blood pressure (mmHg)	118.42 ± 12.99	124.32 ± 13.36	128.68 ± 13.4	130.11 ± 14.14	< 0.0001
Diastolic blood pressure (mmHg)	74.21 ± 9.07	77.39 ± 9.17	80.03 ± 9.48	79.79 ± 9.77	< 0.0001
Fasting glucose (mg/dL)	92.83 ± 14.15	99.46 ± 22.99	104.89 ± 22.66	113.95 ± 32.58	< 0.0001
Waist circumference (cm)	77.94 ± 7.98	82.92 ± 7.63	85.28 ± 7.93	87.51 ± 8.21	< 0.0001
BMI (kg/m^2)	22.9 ± 2.75	24.65 ± 2.87	25.24 ± 3.02	26.11 ± 3.18	< 0.0001
Total cholesterol (mg/dL)	194.29 ± 33.22	202.03 ± 35.71	203.64 ± 40.39	195.83 ± 41.85	< 0.0001
ALT* (mg/dL)	20.53 (20.52–20.54)	23.91 (23.88–23.95)	26.92 (26.89–26.95)	27.21 (27.18–27.24)	< 0.0001
AST* (mg/dL)	23.54 (23.54–23.55)	25.39 (25.37–25.42)	26.76 (26.74–26.78)	27.18 (27.16–27.2)	< 0.0001
GTP* (mg/dL)	24.47 (24.46–24.49)	31.01 (30.94–31.07)	35.17 (35.11–35.22)	35.62 (35.57–35.67)	< 0.0001

Values are expressed as means ± standard deviations, as numbers (%),and as geometric means and 95% confidence intervals for skewed distributions. Comparisons were made using the independent *t*-test (continuous variables) or χ^2 test (dichotomous variables). We defined low income as household income ≤ 20% of the median. HDL, high-density lipoprotein; LDL, low-density lipoprotein

3.2. Risk of psoriasis according to changes in diagnosis of MetS or its components

Table 2 shows differences in psoriasis risk based on changes in the diagnosis of MetS from 2009 to 2012. Compared with the control group, the risk of psoriasis did not increase significantly in the pre-MetS group (HR, 1.001; 95% CI, 0.956–1.048), but increased significantly in the post-MetS (HR, 1.084; 95% CI, 1.045–1.124) and continuous (HR, 1.106; 95% CI, 1.068–1.145) groups.

Table 2. Multivariable HRs of psoriasis risk according to MetS diagnosis changes (CI, confidence interval; HR, hazard ratio)

	n	Cases	Person-years	Incidence rate[a]	HR (95% CI)	
					Model 1	Model 2
Metabolic syndrome						
Control	3,439,976	15,149	4,792,187.9	3.16119	1 (ref.)	1 (ref.)
Pre-MetS	430,044	2,187	608,733.5	3.59271	1.013 (0.968–1.06)	1.001 (0.956–1.048)
Post-MetS	752,360	4,055	1,057,355.48	3.83504	1.101 (1.063–1.14)	1.084 (1.045–1.124)
Continuous-MetS	1,021,944	6,113	1,464,007.41	4.17553	1.13 (1.095–1.167)	1.106 (1.068–1.145)

Values are expressed as HRs (95% CIs) based on Cox proportional hazard regression analysis. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, drinking, exercise, and BMI. [a]per 1,000 person-years. BMI, body mass index; CI, confidence interval; HR, hazard ratio; MetS, metabolic syndrome.

Table 3 shows differences in psoriasis risk based on changes in MetS diagnosis criteria from 2009 to 2012. For the waist circumference criterion, after adjusting for age, sex, smoking, drinking, exercise, and BMI, we found significant increases in psoriasis risk in the pre-MetS (HR, 1.052; 95% CI, 1.003–1.105), post-MetS (HR, 1.089; 95% CI, 1.041–1.139), and continuous-MetS (HR, 1.146; 95% CI, 1.097–1.197) groups, compared with the control group. For the TG criterion, the pre-MetS (HR, 0.99; 95% CI, 0.95–1.031) group had a risk similar to that of the control group, but both the post-MetS (HR,1.091; 95% CI, 1.054–1.13) and continuous-MetS (HR, 1.087; 95% CI, 1.054–1.12) groups had higher risks than the control group. For the HDL criterion, the pre-MetS (HR, 1.063; 95% CI, 1.02–1.107), post-MetS (HR, 1.081; 95% CI, 1.044–1.12), and continuous-MetS (HR, 1.1; 95% CI, 1.064–1.137) groups all had higher psoriasis risks than the control group. For the blood pressure criterion, we found a decreased psoriasis risk in both the pre-MetS and continuous-MetS groups, but no significant no differences in the post-MetS group, compared with the control group. Finally, for the fasting glucose criterion, we found similar risks in all groups.

Table 3. Multivariable HRs of psoriasis risk according to MetS component diagnosis changes (CI, confidence interval; HR, hazard ratio)

	n	Cases	Person-years	Incidence rate[a]	HR (95% CI)	
					Model 1	Model 2
Waist circumference criterion						
Control	4,088,699	18,851	5,727,299.33	3.29143	1 (ref.)	1 (ref.)
Pre-MetS	364,325	1,977	517,279	3.82192	1.053 (1.004–1.103)	1.052 (1.003–1.105)
Post-MetS	497,596	2,607	697,897.52	3.73551	1.09 (1.046–1.135)	1.089 (1.041–1.139)
Continuous-MetS	693,704	4,069	979,808.44	4.15285	1.148 (1.109–1.188)	1.146 (1.097–1.197)
Blood pressure criterion						
Control	2,409,678	10,693	3,349,388.08	3.19252	1 (ref.)	1 (ref.)
Pre-MetS	626,555	2,976	877,496.73	3.39147	0.969 (0.93–1.01)	0.959 (0.92–0.999)
Post-MetS	803,418	3,944	1,126,354.87	3.50156	0.991 (0.955–1.029)	0.975 (0.939–1.012)
Continuous-MetS	1,804,673	9,891	2,569,044.62	3.85007	0.984 (0.956–1.014)	0.965 (0.936–0.996)
Fasting glucose criterion						
Control	3,027,414	13,871	4,242,530.62	3.26951	1 (ref.)	1 (ref.)
Pre-MetS	632,259	3,080	884,471.37	3.48231	0.994 (0.956–1.034)	0.99 (0.952–1.03)
Post-MetS	895,509	4,498	1,256,739.64	3.5791	1.013 (0.979–1.048)	1.003 (0.969–1.038)
Continuous-MetS	1,089,142	6,055	1,538,542.66	3.93554	1.026 (0.994–1.058)	1.013 (0.982–1.046)
Triglyceride criterion						
Control	2,821,098	12,422	3,941,399.88	3.15167	1 (ref.)	1 (ref.)

Pre-MetS	586,456	2,876	830,112.1	3.46459	1.005 (0.964–1.047)	0.99 (0.95–1.031)
Post-MetS	842,109	4,427	1,181,705.98	3.74628	1.11 (1.073–1.149)	1.091 (1.054–1.13)
Continuous-MetS	1,394,661	7,779	1,969,066.33	3.9506	1.117 (1.085–1.15)	1.087 (1.054–1.12)
HDL cholesterol criterion						
Control	3,311,289	14,804	4,599,182.21	3.21883	1 (ref.)	1,(ref.)
Pre-MetS	549,260	2,800	778,582.81	3.59628	1.076 (1.033–1.12)	1.063 (1.02–1.107)
Post-MetS	818,734	4,373	1,154,553.07	3.78761	1.101 (1.064–1.139)	1.081 (1.044–1.12)
Continuous-MetS	965,041	5,527	1,389,966.2	3.97636	1.126 (1.09–1.164)	1.1 (1.064–1.137)

Values are expressed as HRs (95% CIs) based on Cox proportional hazard regression analysis. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, drinking, exercise and BMI. [a]per 1,000 person-years. BMI, body mass index; CI, confidence interval; HR, hazard ratio; MetS, metabolic syndrome.

3.3. Relationship between changes in the number of MetS components at first and second visits and the risk of psoriasis

Next, we plotted our data to visualize the risk of psoriasis according to changes in the numbers of MetS components from 2009 to 2012 (Fig. 1). Regardless of the number of MetS components in an individual in 2009, the psoriasis risks were increased in those with MetS component increases in 2012.

4. Discussion

In this large-scale nationwide population-based study, we calculated the psoriasis risks based on MetS diagnosis changes over a period of 4 years. Our results showed that the psoriasis risk in the pre-MetS group was similar to that in the control group; however, the risks were greater in the post-MetS and continuous-MetS groups than in the control group. This tendency was slightly different for each component of the MetS. First, for the waist circumference criterion, the psoriasis risk was higher in all

three groups (pre-MetS, post-MetS, and continuous-MetS) than in the control group. For TG and HDL cholesterol criteria, the psoriasis risk was increased only in the post-MetS and continuous-MetS groups. For the fasting blood glucose criterion, the psoriasis risks were similar in all groups. Finally, for the blood pressure criterion, the risk of psoriasis decreased in the pre-MetS and continuous-MetS groups.

Many reports have studied the association between psoriasis and MetS, but most of those studies were designed to evaluate the risk of MetS in patients with psoriasis[5,14–22]. To our knowledge, there have been few reports concerning the risk of psoriasis in patients with MetS[8,9,23]. One such report described a large-population based cross-sectional study involving 34,996 individuals, which was published by a Norwegian research team in 2018[9]. The relative risk of psoriasis in the individuals with MetS was 1.66, compared with the control group. They also examined the associations of each MetS criterion with the development of psoriasis and found increased psoriasis risks in patients with waist circumference, TG, and HDL components, but not in those with high blood pressure or blood glucose levels. Those results are consistent with our findings.

Our study differs from others in that the patients with MetS were followed for a period of 4 years, and were divided into four groups for systematic analysis of the associations between psoriasis and MetS components. In the pre-MetS group, we found similar psoriasis risks in the control group, but the post-MetS and continuous-MetS groups had significantly higher psoriasis risks than the control group. This trend was consistent for the waist circumference and TG MetS components. For the HDL criterion, the HR was higher in the post-MetS and continuous-MetS group than in the pre-MetS group. This implies that components of MetS, particularly obesity and dyslipidemia, may influence the development of psoriasis.

The association between psoriasis and MetS has been reported, but it is unclear whether one of the two conditions precedes or induces the other[9]. Central obesity and dyslipidemia contribute to an increased psoriasis risk. Several hypotheses have been suggested to explain the increased psoriasis risk in individuals with MetS. A convincing hypothesis is that the increasing levels of inflammatory markers in MetS lead to the increased psoriasis risk. MetS and psoriasis share inflammatory pathways, such as the T helper-17-mediated or T helper-1-mediated inflammation pathways[3]. Many similar cytokines contribute to the pathogeneses of psoriasis and impaired lipoprotein regulation[24,25]. Moreover, patients with central obesity have excessive adipose tissue, which secretes adipokines, drivers of various chronic inflammation processes such as psoriasis[26]. Another hypothesis states that the two diseases share genetic loci. One study demonstrated shared genes between psoriasis and dyslipidemia, hypertension, and coronary artery disease[27], but other studies have found no genetic associations between psoriasis and MetS or coronary artery disease[27–30]. Our findings that psoriasis risk was decreased in the pre-MetS group supported the hypothesis that persistently elevated inflammatory markers in MetS lead to an increased risk of psoriasis. The inflammation in MetS differs from the traditional concept of tumor, redness, pain, and heat. It is helpful to characterize MetS inflammation as “low-grade” or chronic. The condition is primarily caused by nutrient and metabolic excesses, which trigger various pathologic mechanisms (e.g., Toll-like receptor pathways or inflammasomes such as NLRP3 activation[31]) that are

also increased in psoriasis[32,33]. Therefore, we infer that the continually increased inflammation in MetS plays a role in the development of psoriasis.

Additionally, we analyzed the associations of MetS components with psoriasis risk. For the waist circumference component, the HR in the continuous-MetS group was 1.146 (95% CI, 1.097–1.197), the strongest association compared with those of other MetS components. This was followed by the associations of HDL (HR, 1.106; 95% CI, 1.068–1.145) and TG (HR, 1.013; 95% CI, 0.982–1.046). The fasting glucose component did not show a significant association with psoriasis risk, and the blood pressure component was associated with lowered risk in both the pre-MetS and continuous-MetS groups, compared with the control group. These results differ from those of other studies, which showed positive associations between psoriasis risk and all MetS components[8,21,34,35]. Other recent, large, well-designed studies showed that dyslipidemia and abdominal obesity were the main MetS components positively associated with psoriasis risk; however, they found no significant associations of the MetS components of blood pressure and fasting glucose level with psoriasis risk[9,14, 18–20,22,36], consistent with our results.

The strength of our study lies in its large cohort size, which was representative of the entire Korean population; therefore, the findings are likely to be generalizable to the general public in Korea. In addition, by dividing the MetS patients into four groups based on MetS improvements or aggravations, we were able to characterize the causal relationship between MetS and psoriasis. In addition, we were able to adjust our regressions for confounding factors, such as smoking, drinking, physical activity and BMI, which were included in the source database. However, there was a notable limitation in this study. Because the diagnosis of MetS and psoriasis was dependent on ICD-codes, coding or misclassification errors may have been included. However, a study verifying the frequency of such errors found that approximately 70% of the diagnostic codes were consistent with those in the medical records[10].

Conclusions

Our findings from this population-based, cross-sectional study in Korea demonstrated the effects of changes in MetS diagnosis on psoriasis risk. Our study differs from prior investigations because we focused on MetS diagnosis changes, and our results can help to better elucidate the association between psoriasis and MetS. Remarkably, the risk of psoriasis was higher in patients with sustained or newly induced MetS than in those without MetS (regardless of prior MetS status). Therefore, we emphasize the need to personally explain these findings to patients.

Declarations

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Declarations of interest: none

Author contributions

HJ Lee: Writing – original draft, KD Han: Data Curation, HE Park: Writing – review and editing, JH Han: Writing – Review and editing, CH Bang: validation, YM Park: conceptualization, JH Lee: conceptualization and supervision

Data Availability Statement

The data used in this study are owned by the Korean National Health Insurance Service, and the public sharing of these data is restricted. The authors accessed these data after requesting them from the National Health Insurance Data Sharing Service (NHISS). The authors of this study enjoyed no special access privileges before requesting the data, and they confirm that other qualified researchers should also be able to request access to these data from the NHISS. For more information about this process, please see https://nhiss.nhis.or.kr/bd/ab/bdaba032eng.do.

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Figures

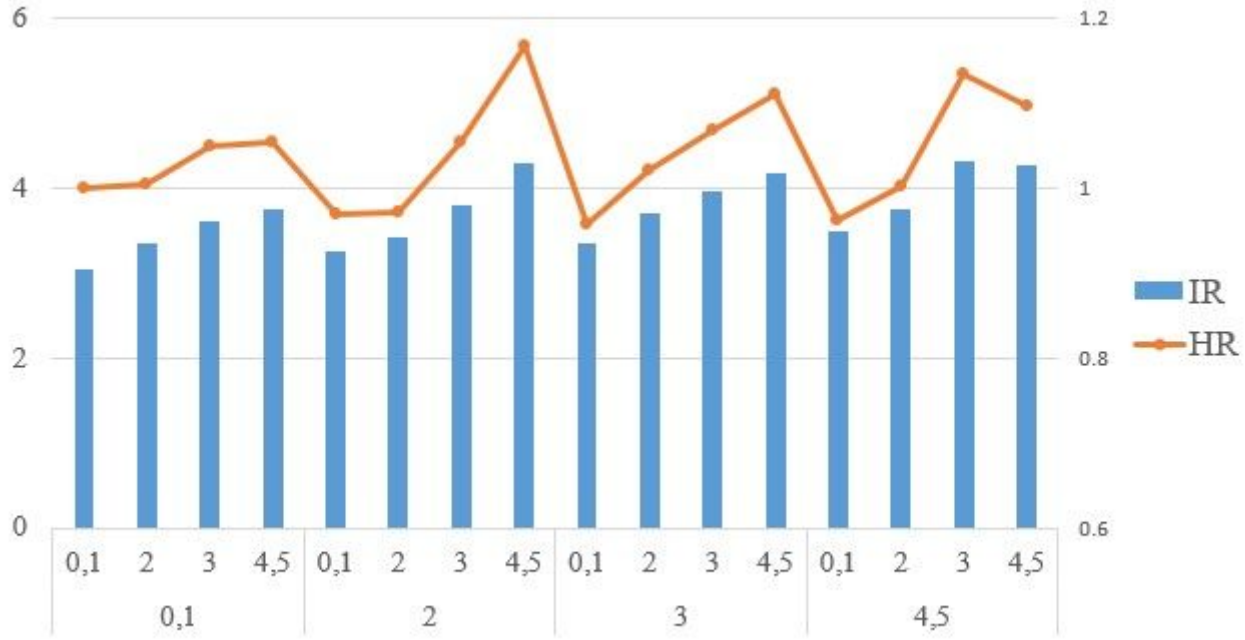

Figure 1

Relationship between changes in the number of MetS components from first to second visits and the risk of psoriasis