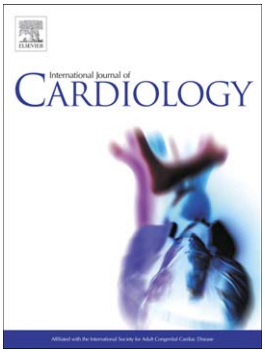

Somatic symptoms of anxiety and nonadherence to statin therapy

Maarit Jaana Korhonen, Jaana Pentti, Juha Hartikainen, Mika Kivimäki, Jussi Vahtera

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TITLE

Somatic symptoms of anxiety and nonadherence to statin therapy

AUTHORS

Maarit Jaana Korhonen, PhD, Senior Researcher[1]; Jaana Pentti, BSc, Statistician[2], Juha Hartikainen, MD, PhD, Professor[3]; Mika Kivimäki, PhD, Professor[4]; Jussi Vahtera, MD, PhD, Professor[5]

AFFILIATIONS

[1]Department of Public Health, University of Turku, Turku, Finland and Division of Pharmaceutical Outcomes and Policy, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA

[2]Finnish Institute of Occupational Health, Turku, Finland

[3]Heart Center, Kuopio University Hospital and School of Medicine, University of Eastern Finland, Kuopio, Finland

[4]Department of Epidemiology and Public Health, University College London, London, UK

[5]Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland

STATEMENT OF AUTHORSHIP

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented, and the interpretation thereof.

CORRESPONDING AUTHOR

Maarit Jaana Korhonen; Department of Public Health, FI-20014 University of Turku, Finland; E-mail: maarit.korhonen@utu.fi; Tel. +358 40 357 2081

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CONFLICT OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

Keywords: statins, medication adherence, symptoms, anxiety

ABSTRACT

Background

The association between anxiety and nonadherence to preventive therapies remains unclear. We investigated whether somatic symptoms of anxiety predict statin nonadherence.

Methods

This is a prospective cohort study of 1924 individuals who responded to a questionnaire survey on health status and initiated statin therapy after the survey during 2008-2010. We followed the cohort for nonadherence, defined as the proportion of days covered <80%, during the 365 days since the first dispensation after the survey. We used log-binomial regression to estimate the predictors of nonadherence.

Results

18% of participants reported no experience of the eight somatic symptoms of anxiety (palpitation without exercise, irregular heartbeat, chest pain upon anger or emotion, sweating without exercise, flushing, tremor of hands or voice, muscle twitching) before the statin initiation, and 16% had experienced at least one symptom on average weekly to daily. 49% of respondents were nonadherent. Weekly to daily occurrence of these symptoms predicted a 33% increase in the risk of nonadherence (risk ratio [RR] 1.33, 95% confidence interval, CI, 1.13-1.57) compared to no symptoms when adjusted for sociodemographics, lifestyle risks, cardiovascular comorbidities, and depression. Particularly, chest pain upon anger or emotion (RR 1.21, 95% CI 1.01-1.46) and muscle twitching (RR 1.24, 95% CI 1.08-1.42) predicted an increased risk of nonadherence to statin therapy. Psychological symptoms of anxiety were not associated with nonadherence when adjusted for somatic symptoms.

Conclusions

Somatic anxiety-related symptoms predicted nonadherence to statin therapy. Information on pre-existing somatic symptoms may help identifying patients at increased risk of statin nonadherence.

INTRODUCTION

Hypercholesterolemia is one of the most common chronic conditions affecting approximately 40% of the adult population globally [1]. Large randomized controlled trials and meta-analyses provide convincing evidence for the benefits of lowering low-density lipoprotein cholesterol by statins in the primary and secondary prevention of cardiovascular events [2, 3]. The effectiveness and cost-effectiveness of statin therapy, however, depends on the extent to which patients adhere to their statin therapy [4-6]. The average prevalence of nonadherence to statin therapy, often defined as the proportion of days covered (PDC) by the dispensed statin tablets less than 80%, is almost 50% [4,7].

Despite extensive research, reliable indicators for nonadherence to statin therapy have not been found [7, 8]. Large healthcare utilization database studies suggest that statin nonadherence is more common in patients free of established cardiovascular disease (CVD), hypertension or diabetes, among those from low income groups or with high out-of-pocket costs, and when there is a lack of lipid monitoring [7,9]. Also mood disorders, such as depression and anxiety, may influence patients' preferences and capacity to adhere to medication as these disorders affect patients' motivation, cognitive function, and energy [10]. For example, a meta-analysis of US studies on medication adherence among patients with chronic conditions found that depressed patients have almost twice the odds of being nonadherent to their antihypertensive or lipid-lowering medication compared to their nondepressed counterparts [11], although database studies employing objective adherence measures based on pharmacy records, such as PDC, have reported somewhat weaker associations between depression and nonadherence to statin therapy [8, 12-14].

Anxiety is a heterogeneous disorder ranging from panic to obsessive-compulsive disorder and generalized anxiety about health; it may also be associated with nonadherence to preventive cardiovascular medication although this association is not necessarily straightforward [10]. Being anxious about one's health and fear of complications of the condition being treated can promote adherence while concerns about potential adverse effects of the medication can lead to nonadherence [15]. One cross-sectional study found that hypertensive patients with high anxiety sensitivity, that is, fear of the negative social, physical or cognitive

consequences of anxiety-related sensations, had almost double the likelihood of being nonadherent to their antihypertensive medication compared to those with low anxiety sensitivity [16]. Every second patient with high anxiety sensitivity reported having experienced adverse drug effects while less than one in four patients with low anxiety sensitivity reported them. Among patients who have discontinued their statin therapy, perceived harmful effects from statins or fear of them are the most commonly reported reasons for discontinuing the therapy [17-19].

Anxiety is a multidimensional concept with cognitive, emotional and biological domains [20, 21], but it appears that the tendency to experience neurovegetative symptoms associated with anxiety, such as palpitation, sweating, trembling, chest pain and hot flushes or cold chills [21], may be particularly relevant in terms of nonadherence. However, we are not aware of any studies that have investigated the association between these somatic anxiety-related symptoms and nonadherence to statin therapy. The aim of the current study is therefore to investigate whether somatic symptoms of anxiety predict future nonadherence to statins.

MATERIALS AND METHODS

Population and design

This study is a part of the Finnish Public Sector (FPS) study, an ongoing cohort study of employees of ten towns and six hospital districts who had a job contract for at least six months during the years 1991-2005 [22]. Subcohorts nested within this register cohort have been targeted by questionnaire surveys in 2/4-year intervals since 2000. The present study included those cohort members who were employed by the ten towns and responded to the 2008/09 survey that for the first time collected information on somatic symptoms of anxiety (42,877 responded; response rate 69%). We linked the participants' responses to the survey to records of filled statin prescriptions using personal identification numbers and then restricted the sample to those participants who began statin therapy after the survey. A new statin user refers to an individual who had not filled any statin prescriptions within 365 days preceding the survey. With these inclusion criteria the analytic cohort of this study includes 1924 new statin users who had full data on statin dispensations for 12 months (365 days) by the end of follow-up (Dec 31, 2011).

According to the Finnish law, there is no requirement for written consent for register-based and survey research, as long as participation is voluntary. The participants of the FPS study were informed about the aims of the study and the possible record linkages. Participants' information was anonymized and de-identified prior to analyses. The Ethics Committee of the Helsinki and Uusimaa Hospital District approved the study

Somatic symptoms of anxiety

Autonomic arousal is common among individuals liable to anxiety [21]. For example, in the diagnoses of generalized anxiety disorder the following somatic symptoms are emphasized: symptoms of autonomic arousal (palpitation, sweating, trembling, dry mouth), chest and abdominal symptoms (difficulty breathing, feeling of choking, chest pain, nausea), and general symptoms (hot flushes or cold chills, numbness or tingling, muscle tension, restlessness and inability to relax, difficulty swallowing) [21]. The FPS study assessed somatic anxiety-related symptoms with an 8-item scale focusing on symptoms of sympathetic nervous system activation [23]. The participants were requested to report occurrence of the following eight symptoms during the past month: 1) "Palpitation without exercise," 2) "Irregular heartbeat," 3) "Chest pain upon anger or emotion," 4) "Sweating without exercise," 5) "Flushing," 6) "Tremor of hands," 7) "Tremor of voice," 8) "Muscle twitching." The answer choices for each item were: daily or almost daily, weekly, less often, never. The answer choices were assigned values from 0 to 3. The mean score of the eight items was calculated and divided into three categories (0=never, 0<less often than weekly<1, >1=weekly to daily). When calculating the mean symptom score, missing information on an individual item was coded as 0. The scale has shown adequate psychometric properties (Cronbach α=0.77; 5-year test-retest reliability r=0.59) [23].

Nonadherence to statin therapy

The outcome of interest was nonadherence to statins (Anatomical Therapeutic Chemical [ATC] code C10AA), measured by PDC during the 365 days since the first dispensation in 2008-2010. Data on filled

statin prescriptions came from the Finnish Prescription Register, pharmacy-claims database managed by the Social Insurance Institution of Finland (SII) [24]. The database contains records of all medications that are dispensed and reimbursed under the National Health Insurance Scheme. For each medication, the dispensing date, the ATC classification code [25] and the quantity dispensed are recorded. Information on prescribed dose or duration of therapy is not available in a structured format; therefore, we calculated the days' supply in each dispensation on the assumption of one tablet per day [26]. We defined nonadherence as PDC <80%. The threshold of 80% is a widely used both by adherence research [4] and many quality measures [27], and it corresponds to the level of statin adherence above which patients with coronary artery disease have been shown to benefit from statin therapy [28].

The National Health Insurance Scheme provides prescription drug coverage for all ~5.4 million non-institutionalized residents of Finland. The current reimbursement system has three categories (basic, lower special, and higher special refund) graded according to medical criteria based on the severity of the illness and the necessity of the drug therapy [29]. Statins are available by prescription only, and they are reimbursed under the basic refund category; however, patients with familial hypercholesterolemia or coronary artery disease are eligible for lower special refund. During the study years, the reimbursement was 42% and 72% of the price of the statin in the basic and lower special refund categories, respectively. Statin therapy was typically started with low-cost generic simvastatin (for 97% of new users in 2008 [30]; therefore, statin costs are likely to have only a minor impact on adherence in our study.

Covariates

We included age, sex, marital status, and education as sociodemographic covariates. Statistics Finland provided information on the level of education (vocational or basic education vs. university or college degree) [31] while information on marital status (married or cohabiting vs. single, divorced, or widowed) came from the survey responses. We classified participants as current smokers if they reported smoking daily or almost daily at the time of the survey. Extreme drinking occasions were identified by asking the participants whether they had passed out due to heavy drinking during the past 12 months. Heavy alcohol use was defined as consuming >210 grams of pure alcohol/week [32] based on the habitual frequency and

amount of beer, wine, and spirits intake reported by the participants. Physical activity was measured by the Metabolic Equivalent Task (MET) index and expressed as the summed score of MET hours/day. Reporting <2 MET hours per day indicated physical inactivity. Self-reported weight and height were used to determine body mass index (BMI) and obesity (BMI $\geq$30 kg/m^2). Finally, we used a binary variable (any of the five risk factors vs. none) to indicate the presence of lifestyle risks.

Information on comorbid cardiovascular conditions came from the SII Special Refund Register and the Finnish Care Register. Presence of a comorbid condition was defined as entitlement to special refund for medication costs due to diabetes mellitus, chronic hypertension, heart failure, or coronary artery disease at statin initiation, any hospitalization for these conditions, stroke, or arrhythmia during 36 months before statin initiation.

Depression was defined as filling of one or more prescriptions for antidepressants (ATC code N06A), hospitalization or sick leave for depression during 36 months before statin initiation. Psychological symptoms of anxiety were measured by the Spielberger State-Trait Anxiety Inventory [33]. Trait anxiety refers to the general tendency for experiencing anxiety while state anxiety reflects the intensity of anxiety experienced at the time of measurement. In the 2008/09 FPS survey, a short form including six items of trait anxiety was administered (example of an item: "I feel nervous and restless"). Scores for each item ranged from 1, almost never, to 4, almost always. We defined the trait anxiety level as low, intermediate, or high using the first and the third quartiles of the total score as the cut-off points.

Statistical analyses

We estimated the risk ratios (RR) for nonadherence and their 95% confidence intervals (CI) with log-binomial regression models. The models were first adjusted for age (at statin initiation) and sex (Model 1), and then further for marital status, education, presence of lifestyle-related risks, cardiovascular comorbidities, and depression (Model 2). Finally, Model 3 included also trait anxiety. The numbers of

participants included in the symptom specific analyses vary as those participants missing data on the somatic anxiety-related symptom in question or covariates were excluded from these analyses.

As the determinants of nonadherence may vary by sex [34-36], we tested for sex-differences in the associations between the frequency and type of somatic symptoms and nonadherence by including the interaction term "sex*symptom frequency/type" in the age-adjusted models. To further examine variations in the associations between the frequency/type of somatic symptoms and nonadherence across the subgroups defined by age (<60 vs. ≥60 years), marital status, education, presence of lifestyle risks, cardiovascular comorbidities and depression we included the interaction terms "subgroup*symptom frequency/type" in the age-sex-adjusted models. Generally, P values <0.05 were interpreted as statistically significant. All statistical analyses were conducted with SAS 9.2 statistical software (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

The study population included 1924 individuals who responded to the survey in 2008/09 and after that began statin therapy by the end of 2010. Seventy-two percent of the study population were women, and the mean age was 56.3 (standard deviation, SD=7.3) years (Table 1). Eighteen percent reported that they had not experienced any of the eight somatic symptoms of anxiety during the preceding month, and 16% had experienced them on average weekly to daily. The mean score of these symptoms was 0.56 (SD=0.54). The score was higher among women than men and among those who were not married or cohabiting. Also those with lifestyle risks, comorbid cardiovascular conditions, depression or higher levels of trait anxiety had higher mean scores than those without these conditions. The most common symptoms experienced at least weekly were sweating without exercise (38%) and flushing (23%).

The proportion of participants who were nonadherent during the first 365 days since initiation of statin therapy was 49%. There was a graded increase in the risk of nonadherence according to the mean score of somatic symptoms of anxiety (Table 3). After adjustment for sociodemographic characteristics, lifestyle risks, cardiovascular comorbidities and depression prior to statin initiation, those experiencing somatic

anxiety-related symptoms on average weekly to daily had a 33% greater risk of nonadherence to statin therapy (95% CI 13%-57%) in comparison with those who reported no symptoms. Further adjustment for trait anxiety only slightly attenuated the association between the frequency of somatic symptoms and the risk of nonadherence (Table 3). Conversely, a three-category measure of trait anxiety predicted nonadherence weakly in a model adjusted for the same covariates; compared with those with the lowest level of trait anxiety, adjusted RRs were 0.94 (95% CI 0.84-1.05) for those with intermediate and 1.16 (1.02-1.32) for those with high trait anxiety levels. When adjusting for the frequency of somatic anxiety-related symptoms, these associations were further attenuated (RR 0.91, 95% CI 0.81-1.02, for intermediate and RR 1.08, 95 CI 0.94-1.24, for high levels of trait anxiety). Also the association between depression and nonadherence was slightly weakened when adjusted for somatic anxiety-related symptoms; when adjusting for sociodemographics, lifestyle risks and cardiovascular comorbidities, RR was 1.12 (1.01-1.26) and when further adjusting for the frequency of somatic symptoms of anxiety, it was 1.09 (0.97-1.22).

The graded increase in the risk of nonadherence to statin therapy with increasing frequency of somatic anxiety-related symptoms was seen in the majority of the subgroups of the study population (Figure 1; Table A.1). However, significant variation in these associations was observed according to the presence of comorbid cardiovascular conditions (*P* for interaction 0.03). Weekly to daily occurrence of somatic anxiety-related symptoms almost doubled the risk of nonadherence when compared with no symptoms (age-sex-adjusted RR 1.90, 95% CI 1.35-2.70) among those with cardiovascular comorbidities but no such increase was observed among those free of cardiovascular comorbidities (RR 1.17, 95% CI 0.97-1.40).

We also analyzed the associations between each of the eight somatic symptoms and the risk of nonadherence separately (Table 3). When compared with less than weekly or no occurrence, weekly to daily occurrence of chest pain upon anger or emotion and muscle twitching predicted a ~20% increase in the risk of nonadherence even after adjustment for sociodemographic characteristics, lifestyle risks, cardiovascular comorbidities and depression. Adjustment for trait anxiety attenuated the associations between individual symptoms and the risk of nonadherence. We observed no significant variation in the associations between

any individual somatic anxiety-related symptom and nonadherence by sex, age, presence of lifestyle risks or cardiovascular comorbidities (P for interaction terms >0.05, Table A.2). Among those who were not married or cohabiting, weekly to daily experiences of tremor of hands or voice predicted over 40% increase in the risk of nonadherence while no increase was observed among those who were married or cohabiting (P for interactions <0.05). Among those with university or college education, daily to weekly experiences of irregular heartbeat were associated with a 24% increase in the nonadherence risk but not among those with lower educational level (P=0.048). Finally, among those with depression, sweating without exercise predicted a 24% increase in the risk of nonadherence but no increase among nondepressed participants (P=0.04).

DISCUSSION

This study involving over 1900 new statin users in Finland suggests that somatic symptoms of anxiety are associated with nonadherence to statin therapy. Experiencing these symptoms at least weekly increases the risk of nonadherence to statin therapy by 33% in comparison with not experiencing such symptoms. With the risk of nonadherence being almost 50%, this translates to ~15 percent unit increase in the risk of nonadherence. Also trait anxiety increases the risk of nonadherence but to a lesser extent, and the frequency of somatic anxiety-related symptoms predict nonadherence even after adjustment for trait anxiety. Trait anxiety had no such association with nonadherence independent of somatic symptoms. Of the specific somatic symptoms, particularly chest pain upon anger or emotion and muscle twitching predict nonadherence to statin therapy. Furthermore, the increased risk of nonadherence in association with somatic symptoms of anxiety does not seem to be limited to any specific subgroup of new statin users.

The high rate of nonadhence to statin therapy in the present study is comparable to the rates reported by previous studies for all new statin users in Finland between 2000-2004 [8] and those with diabetes between 2005-2008 [37] and by previous research elsewhere [7]. Also the association between depression and statin nonadherence is similar to those reported by previous database studies [8, 12-14]. In prior research, the results on the association between anxiety and nonadherence to preventive cardiovascular medication have

been mixed [10]. Our findings on the increases in the risk of nonadherence in relation to anxiety are supported by studies using self-reported measures of anxiety [38, 39], while diagnosed anxiety disorder has been linked with a decreased risk of nonadherence [40]. Furthermore, a few studies have found those using anxiolytic medications to be less likely to discontinue their statin use [41, 42] which suggests that alleviation of symptoms of anxiety might promote adherence. Dempe et al. [39] suggested that state and trait anxiety may have opposite effects on medication nonadherence among patients with coronary artery disease. Our results on the associations between somatic symptoms of anxiety and trait anxiety with statin nonadherence support the notion that the relationships with nonadherence may vary across anxiety-related symptoms.

Somatic anxiety-related symptoms seem to be common as four in five respondents reported experiencing them at least some times and 16% daily to weekly. Patients with these symptoms may be more likely to misattribute their regular physiological reactions to their statin and consequently stop or avoid taking it [16]. Former statin users have reported symptoms such as gastrointestinal discomfort and increased heart rate among the reasons for deciding to discontinue the therapy [18, 43]. Alternatively, patients with somatic symptoms of anxiety may be overly vigilant of the true adverse effects associated with statins, such as muscle pain, that affect the same sites as their pre-existing symptoms. In an Internet-based survey of over 10,000 current and former statin users, almost 30% of the respondents reported muscle-related adverse effects. Of the former statin users, 60% had experienced muscle-related effects while altogether 62% reported side-effects as the reason for discontinuation of statin therapy [19]. Our observations together with the previous studies suggest that new statin users could benefit from a detailed discussion about the potential and perceived adverse effects from statins with a healthcare professional.

Strengths and limitations

This is the first study to examine the associations between somatic anxiety-related symptoms and nonadherence to statins. We used an objective measure of nonadherence that is not affected by social desirability and recall biases; however, we may have underestimated nonadherence as we were not able to confirm whether the dispensed statins were actually ingested. Another limitation is the lack of information

on adverse events after statin initiation and the reasons for nonadherence or discontinuation of therapy [19]. People with most severe anxiety or anxiety-related symptoms and potentially highest rates of nonadherence may be less likely to participate in a survey than those with milder anxiety. In addition, missing data for individual survey items among the participants may not be randomly distributed. In our sample, however, the number of participants with missing data was low; 31 persons (1.6%) missed data on trait anxiety and of them, 23 (74%) were classified as nonadherent. The numbers of those who missed data on individual somatic symptoms varied between 15 (0.8%) and 26 (1.4%); and among these nonrespondents the risk of nonadherence was not consistently higher or lower than among respondents. Due to reliance on data from healthcare utilization databases to identify cardiovascular comorbidities and depression, we may have underascertained these conditions. In order to assess the role of residual confounding in our observations, we further adjusted our multivariable models for the presence of psychological distress (measured by the General Health Questionnaire [45]), cancer, use of hormone therapy (women) or antihypertensive medications, and the number of self-reported childhood adversities [36]; however, the RRs did not change appreciably (data not shown). Finally, our study population was a relatively homogenous sample of public sector employees from a country with universal healthcare and drug reimbursements; therefore, the associations between somatic anxiety-related symptoms and nonadherence could be different in other populations with different social and economic barriers to adherence.

CONCLUSIONS

Frequent occurrence of somatic symptoms of anxiety but not psychological symptoms was found to be associated with future nonadherence to statin therapy. Further research is needed to confirm our findings and to investigate whether information on these symptoms could be useful in identification of those at high risk of nonadherence and whether management of these symptoms could improve adherence to statin therapy.

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FIGURE CAPTIONS

Figure 1. Risk of nonadherence (%) and 95% confidence intervals according to frequency of somatic symptoms of anxiety in subgroups of the study population. CVD: cardiovascular comorbidity

Table 1. Baseline characteristics and mean frequency of somatic symptoms of anxiety of the study population.

			Somatic symptoms		
Characteristic	n	%	Mean	SD	*P**
All	1924	100	0.56	0.54	
Sex					<0.0001
Men	543	28	0.48	0.55	
Women	1381	72	0.60	0.54	
Age, years					0.66
29-59	1224	64	0.56	0.53	
60-75	700	36	0.57	0.56	
Married or cohabiting					0.01
No	496	26	0.61	0.59	
Yes	1412	74	0.54	0.52	
Education					0.25
Vocational or basic	1046	54	0.58	0.56	
University or college	878	46	0.55	0.52	
Lifestyle risk					0.02
No	723	38	0.53	0.50	
Yes	1192	62	0.59	0.57	
Comorbid condition†					0.003
No	1256	65	0.54	0.51	
Yes	668	35	0.61	0.59	
Depression					<0.0001
No	1585	82	0.52	0.51	
Yes	338	18	0.79	0.65	
Trait anxiety					<0.0001
Low	528	28	0.32	0.38	
Intermediate	982	52	0.54	0.47	

High	383	20	0.97	0.65
Somatic symptom weekly to daily				
Palpitation without exercise	359	19	-	
Irregular heartbeat	308	16	-	
Chest pain upon anger or emotion	84	4.4	-	
Sweating without exercise	678	36	-	
Flushing	396	21	-	
Tremor of hands	105	5.5	-	
Tremor of voice	74	3.9	-	
Muscle twitching	154	8.1	-	

SD: standard deviation

*Statistical significance of differences between the groups tested using the t-test or analysis of variance.

† Diabetes mellitus, chronic hypertension, coronary insufficiency, coronary heart disease, cardiac arrhythmia, and cerebrovascular disease.

Table 2. Risk ratios of nonadherence among new statin users by the level of somatic symptoms of anxiety.

Symptoms	n (%)	Risk (%)*	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)
Never	341 (18)	42	1.00	1.00	1.00
Less than weekly	1270 (66)	49	1.17 (1.02-1.34)	1.18 (1.02-1.36)	1.18 (1.02-1.37)
Weekly to daily	313 (16)	57	1.32 (1.12-1.54)	1.33 (1.13-1.57)	1.27 (1.06-1.52)

RR=risk ratio; CI=confidence interval

*Risk of nonadherence (proportion of days covered <80%) in a group with a specific frequency of symptoms.

Model 1 adjusted for age and sex.

Model 2 adjusted for age, sex, education, marital status, presence of lifestyle risks, cardiovascular comorbidities, and depression.

Model 3 adjusted for age, sex, education, marital status, presence of lifestyle risks, cardiovascular comorbidities, depression, and trait anxiety.

Table 3. Risk ratios of nonadherence among new statin users by the type of somatic symptoms of anxiety.

Symptom	Risk (%)*	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)
Palpitation without exercise (n=1909)	55	1.14 (1.02-1.27)	1.13 (1.01-1.26)	1.08 (0.96-1.21)
Irregular heartbeat (n=1905)	54	1.11 (0.99-1.25)	1.10 (0.98-1.24)	1.05 (0.93-1.19)
Chest pain upon anger/emotion (n=1898)	61	1.23 (1.03-1.48)	1.21 (1.01-1.46)	1.14 (0.94-1.37)
Sweating without exercise (n=1908)	50	1.05 (0.95-1.15)	1.04 (0.94-1.15)	1.01 (0.92-1.12)
Flushing (n=1905)	53	1.07 (0.96-1.19)	1.08 (0.96-1.19)	1.04 (0.93-1.16)
Tremor of hands (n=1903)	53	1.12 (0.93-1.35)	1.09 (0.90-1.32)	1.02 (0.84-1.24)
Tremor of voice (1903)	55	1.13 (0.91-1.39)	1.10 (0.89-1.36)	1.01 (0.81-1.25)
Muscle twitching (n=1902)	61	1.28 (1.12-1.47)	1.24 (1.08-1.42)	1.19 (1.03-1.37)

RR=risk ratio; CI=confidence interval

* Risk of nonadherence (proportion of days covered <80%) among those with a specific symptom occurring daily to weekly

Comparisons between those with a specific symptom versus no such symptom.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, education, marital status, lifestyle-related risks, cardiovascular comorbidity, and depression.

Model 3: adjusted for age, sex, education, marital status, lifestyle risks, cardiovascular comorbidity, depression and trait anxiety.

Table A.1 Risk ratio (95% confidence intervals) of nonadherence in statin users by the frequency of somatic symptoms of anxiety in subgroups of the study population.

Subgroup	Never	Less than weekly	Weekly to daily	*P* for interaction
All (crude)	1.00	1.19 (1.03-1.36)	1.34 (1.14-1.57)	
All (age-sex-adjusted)	1.00	1.17 (1.02-1.34)	1.32 (1.12-1.54)	
Sex				
Men	1.00	1.02 (0.82-1.28)	1.24 (0.94-1.65)	0.38
Women	1.00	1.25 (1.05-1.50)	1.38 (1.13-1.69)	
Age, years				
29-59	1.00	1.07 (0.91-1.26)	1.25 (1.03-1.51)	0.24
60-75	1.00	1.37 (1.06-1.77)	1.47 (1.09-1.97)	
Married or cohabiting				
No	1.00	1.43 (1.04-1.97)	1.60 (1.13-2.27)	0.32
Yes	1.00	1.11 (0.95-1.29)	1.25 (1.04-1.50)	
Education				
Vocational or basic	1.00	1.21 (1.01-1.46)	1.20 (0.96-1.51)	0.05
University or college	1.00	1.12 (0.91-1.37)	1.49 (1.16-1.83)	
Lifestyle risk				
No	1.00	1.09 (0.88-1.36)	1.33 (1.03-1.73)	0.54
Yes	1.00	1.22 (1.02-1.45)	1.32 (1.08-1.62)	
Comorbid condition†				
No	1.00	1.06 (0.92-1.23)	1.17 (0.97-1.40)	**0.03**
Yes	1.00	**1.58 (1.14-2.19)**	**1.90 (1.35-2.70)**	
Depression				
No	1.00	1.14 (0.98-1.32)	1.32 (1.11-1.58)	0.44
Yes	1.00	1.35 (0.88-2.05)	1.35 (0.87-2.09)	
Trait Anxiety				
Low/intermediate	1.00	1.16 (1.00-1.35)	1.32 (1.08-1.61)	0.53
High	1.00	1.06 (0.69-1.63)	1.06 (0.69-1.64)	

Subgroup-specific risk ratios were computed for a comparison between those with a specific symptom versus those without it and adjusted for age and sex. P-values derived from log-binomial regression models that included the interaction term "subgroup* symptom".

† Diabetes mellitus, chronic hypertension, coronary insufficiency, coronary heart disease, cardiac arrhythmia, and cerebrovascular disease.

Table A.2 Risk ratio (95% confidence intervals) of nonadherence in statin users by the type of somatic symptoms of anxietyin subgroups of the study population.

Subgroup	Palpitation without exercise	Irregular heartbeat	Chest pain upon anger or emotion	Sweating with out exercise	Flushing	Tremor of hands
All (crude)	1.15 (1.03-1.28)	1.11 (0.99-1.24)	1.25 (1.05-1.50)	1.06 (0.97-1.17)	1.09 (0.98-1.22)	1.09 (0.91-1.32)
All (age-sex-adjusted)	1.13 (1.02-1.26)	1.10 (0.98-1.24)	1.24 (1.04-1.49)	1.04 (0.95-1.15)	1.07 (0.96-1.19)	1.11 (0.92-1.33)
Sex	*P*=0.50	*P*=0.32	*P*=0.51	*P*=0.75	*P*=0.42	*P*=0.54
Men	1.04 (0.79-1.37)	0.97 (0.73-1.30)	1.39 (0.98-1.95)	1.01 (0.80-1.27)	1.18 (0.91-1.54)	1.02 (0.71-1.45)
Women	1.15 (1.02-1.29)	1.14 (1.00-1.29)	1.20 (0.98-1.48)	1.05 (0.95-1.17)	1.05 (0.93-1.18)	1.15 (0.93-1.42)
Age, years	*P*=0.98	*P*=0.65	*P*=0.46	*P*=0.64	*P*=0.17	*P*=0.29
29-59	1.13 (0.99-1.29)	1.13 (0.98-1.30)	1.30 (1.06-1.59)	1.06 (0.94-1.19)	1.12 (0.99-1.27)	1.04 (0.82-1.31)
60-75	1.13 (0.82-1.56)	1.19 (0.84-1.68)	1.51 (0.88-2.58)	1.11 (0.84-1.48)	1.32 (0.96-1.83)	0.84 (0.48-1.47)
Married or cohabiting	*P*=0.63	*P*=0.53	*P*=0.65	*P*=0.27	*P*=0.43	***P*=0.03**
No	1.18 (0.97-1.44)	1.04 (0.83-1.31)	1.14 (0.78-1.67)	1.13 (0.95-1.35)	1.14 (0.94-1.38)	**1.43 (1.13-1.80)**
Yes	1.12 (0.98-1.27)	1.13 (0.99-1.29)	1.26 (1.02-1.55)	1.01 (0.90-1.13)	1.03 (0.91-1.18)	0.96 (0.74-1.24)
Education	*P*=0.68	***P*=0.05**	*P*=0.74	*P*=0.48	*P*=0.67	*P*=0.35
Vocational or basic	1.11 (0.96-1.29)	0.98 (0.82-1.17)	1.28 (1.02-1.60)	1.01 (0.89-1.15)	1.09 (0.94-1.26)	1.03 (0.79-1.33)
University or college	1.16 (0.99-1.36)	**1.24 (1.06-1.44)**	1.20 (0.90-1.59)	1.08 (0.94-1.24)	1.04 (0.89-1.22)	1.22 (0.95-1.58)
Lifestyle risk	*P*=0.57	*P*=0.80	*P*=0.84	*P*=0.15	*P*=0.63	*P*=0.06
No	1.09 (0.91-1.30)	1.08 (0.89-1.31)	1.21 (0.86-1.70)	1.14 (0.98-1.32)	1.10 (0.93-1.31)	1.47 (1.12-1.95)
Yes	1.16 (1.01-1.33)	1.12 (0.97-1.29)	1.26 (1.02-1.55)	0.99 (0.87-1.12)	1.05 (0.91-1.20	1.01 (0.80-1.27)
Comorbid condition†	*P*=0.90	*P*=0.31	*P*=0.95	*P*=0.11	*P*=0.41	*P*=0.11
No	1.14 (1.00-1.29)	1.07 (0.93-1.23)	1.25 (1.01-1.53)	0.99 (0.89-1.11)	1.04 (0.92-1.18)	0.99 (0.77-1.28)
Yes	1.15 (0.94-1.41)	1.21 (0.99-1.49)	1.26 (0.90-1.77)	1.18 (0.99-1.41)	1.15 (0.94-1.40)	1.35 (1.03-1.76)
Depression	*P*=0.89	*P*=0.89	*P*=0.80	***P*=0.04**	*P*=0.85	*P*=0.63
No	1.12 (0.99- 1.28)	1.09 (0.95-1.25)	1.25 (0.99-1.56)	0.98 (0.88-1.10)	1.07 (0.94-1.21)	1.13 (0.89-1.42)
Yes	1.10 (0.90-1.35)	1.11 (0.89-1.37)	1.19 (0.89-1.59)	**1.24 (1.01-1.51)**	1.04 (0.84-1.29)	1.03 (0.75-1.40)
Trait Anxiety	*P*=0.14	*P*=0.25	*P*=0.14	P=0.38	*P*=0.81	*P*=0.73
Low/intermediate	1.15 (0.99-1.32)	1.11 (0.95-1.30)	1.35 (1.05-1.73)	1.04 (0.93-1.17)	1.02 (0.89-1.18)	0.98 (0.71-1.37)
High	0.96 (0.81-1.15)	0.97 (0.81-1.16)	1.02 (0.78-1.33)	0.95 (0.80-1.13)	1.05 (0.88-1.25)	1.05 (0.84-1.33)

Subgroup-specific risk ratios were computed for a comparison between those with a specific symptom versus those without it and adjusted for age and sex. P-values derived from log-binomial regression models that included the interaction term "subgroup*symptom".

† Diabetes mellitus, chroni

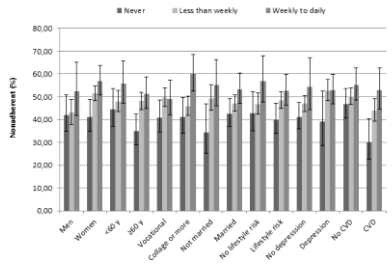

Fig. 1