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Prevalence and determinants of fatigue in the Swiss population: A population based cross-sectional survey

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Abstract

Objective: To assess the prevalence and determinants of fatigue in the general population.

Design: Population based cross-sectional survey performed between May 2014 and April 2017.

Setting: General population of the city of Lausanne, Switzerland.

Participants: 2848 participants (53.2% women, age range 45-86 years).

Primary outcome measure: Prevalence of chronic fatigue, defined as a score ≥4 using the Fatigue severity scale (FSS).

Results: The prevalence of fatigue was 21.9% (95% CI: 20.4% – 23.4%) in the total sample. On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels. Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression, low TSH values, had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad. Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics.

Conclusion: In a population-based sample aged 45 to 86, fatigue was present in one out of five subjects. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea should be assessed first, followed by depression. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step. Sleep complaints and fatigue in older subjects are not a part of aging and should prompt the identification of underlying cause.

Keywords: fatigue; prevalence; epidemiology; Fatigue severity scale

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study assessed the prevalence and determinants of fatigue in a general population setting.
- A large panel of determinants of fatigue was evaluated.
- A list of the most frequent determinants was established, facilitating etiological search in clinical practice
- The study was limited to subjects aged 45 to 86, so that results do not apply to younger or older groups.

INTRODUCTION

Fatigue is usually defined as "an unpleasant physical, cognitive and emotional symptom described as a tiredness not relieved by common strategies that restore energy".[1] Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities .[1] Indeed, fatigue is a common symptom in the general population, with prevalence rates varying between 4 and 45%.[2-4] This ten-fold range in prevalence rates is likely due to the different methods used to assess fatigue.[5]

In healthy subjects, fatigue is a natural occurrence after physical or mental efforts, and is usually relieved by rest.[6] Fatigue is a multidimensional concept, and several determinants have been proposed. Although a cause (somatic or psychiatric) is identifiable in 2/3 of fatigue cases, still 1/3 of cases have no specific diagnosis.[7] The most frequent diagnoses associated with fatigue are viral or upper respiratory tract infection, iron deficiency anemia, adverse effects of medication, and depression or other mental disorder.[8] Fatigue has also been associated with female sex,[6 9] older age [10 11] and lower socioeconomic status,[10 11] although the association with the last two determinants was not found in some studies.[6 12] Importantly, most studies on fatigue have been conducted in selected populations like workers [13] or general practice attendees.[12 14 15] To our knowledge, only two studies have assessed the prevalence of fatigue in the general population [6 16] and only a few have explored the determinants of fatigue in the general population.[9-11 17-19] Also, to date, little is known about the prevalence of fatigue and its determinants in Switzerland.

Hence, this study aimed to examine the prevalence and determinants of fatigue in a population-based sample aged 45-86 years from the city of Lausanne, Switzerland. Our hypothesis was that fatigue would be relatively prevalent and associated with several clinical, biological and sociodemographic characteristics.

POPULATION AND METHODS

Study population

The CoLaus study is a population-based cohort exploring biological, genetic, and environmental determinants of cardiovascular diseases. Detailed descriptions of the study design have been reported elsewhere.[20] Briefly, a non-stratified representative sample of the population of Lausanne was recruited between 2003 and 2006 using the following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate. The first follow-up was performed between April 2009 and September 2012 and the second follow-up between May 2014 and April 2017. As fatigue was assessed only in the second follow-up, data from the second follow-up, which included 4881 or the initial 6773 participants recruited at baseline, was used.

Fatigue scale

Fatigue severity during the last week was assessed by the 9 items Fatigue Severity Scale (FSS).[21] This questionnaire has been validated for a general healthy population in the Swiss setting [22] and has a high test-retest reliability.[5] The questionnaire is composed of nine questions; responses are graded using a Likert scale from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement. The final score is the mean value of the nine responses, and a score ≥4 is considered as having severe fatigue.[21]

Covariates

Socioeconomic and lifestyle variables were collected using a self-administered questionnaire. Smoking status was categorized into never, former and current smoker. Educational level was collected at baseline and categorized as obligatory school, apprenticeship, high school/college or university.

Insomnia was assessed using the Insomnia Severity Index (ISI).[23] a 7-items questionnaire evaluating the nature, severity, and impact of insomnia over the last month; namely difficulties falling sleep, sleep maintenance problems, and early morning awakening,

sleep dissatisfaction, interference of sleep disturbances with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Items were scaled 0-4 and then summed to obtain the global ISI score (range: 0-28). Clinically significant insomnia was defined as an ISI score ≥15 (moderate to severe intensity).[23]

Depression was assessed the CES-D [24] is a 20 items self-report instrument developed for research in the general population is used to assess the severity of depressive symptoms over the past week on a 4-point scale. It was translated into French by Fuhrer and Rouillon.[25] It has been used in other recent epidemiological studies assessing the link between depression and cardiovascular risk factors. The questionnaire is composed of 20 questions; responses are graded using a Likert scale from 0 to 3, where 0 indicates rarely or none of the time (less than one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the 20 responses (possible range is 0-60), and a score ≥16 is considered as a risk for depression.

Self-rated health was assessed by a single question where participants had to rate their current health status from five categories ranging from “very bad” to “very good”. As the number of participants rating their health as “very bad” was very small, they were grouped with the participants who rated their health as “bad”.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight/height^2 and categorized as underweight (BMI<18.5 kg/m^2), normal (18.5≤BMI<25 kg/m^2); overweight (25≤ BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2).

Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist

between 0 and 30° of dorsiflexion. Three measurements were performed consecutively with the right hand and the highest value (expressed in kg) was included in the analyses.

Biological assays were performed by the CHUV Clinical Laboratory on fresh blood samples within 2 hours of blood collection, and additional aliquots were stored at –80°C. All measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland). The following analytical procedures (with maximum inter and intra-batch CVs) were used: high sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by immunoturbidimetric method (Tina-quant 4th generation, Roche Diagnostics, Switzerland) with a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid stimulating hormone (TSH) and free T_4 were assessed by chemiluminescence (ECLIA) on a Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free T_4.

Exclusion criteria

Participants were excluded if they lacked fatigue questionnaire, socioeconomic or clinical covariates and biological measures.

Ethical statement and consent

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-up. The full decisions of the CER-VD can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Statistical analysis

Statistical analysis was performed using Stata version 15.1 for windows (Stata Corp, College Station, Texas, USA). Prevalence rates for fatigue were expressed as percentage and 95% confidence interval (CI). Descriptive results were expressed as number of participants (percentage) for categorical variables or as average±standard deviation for continuous variables. Bivariate analyses were performed using chi-square or Fisher's exact test for categorical variables and student's t-test for continuous variables. All categorical variables significantly associated with fatigue in the bivariate analysis were included in the multivariable analysis. Multivariable analysis was performed using logistic regression with fatigue (dichotomized into yes/no) as dependent variable; results were expressed as Odds ratio (OR) and 95% CI.

As the number of excluded participants was high, sensitivity analyses were conducted by creating a propensity score for being excluded [26]. The propensity score was computed using logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly associated with exclusion as independent variables. A probability of exclusion was computed for each participant, and the inverse of the probability was used for weighting.

Statistical significance was assessed for a two-sided test with $p<0.05$.

Results

Study population

Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most frequent reason was lack of data regarding fatigue. The comparison between included and excluded participants is provided in **supplemental table 1**. Excluded participants were more frequently women, were older, had a lower educational level, were more frequently never or

current smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and hypertension) and rated their health worse.

Prevalence and determinants of fatigue

The overall prevalence of fatigue was 21.9% (95% CI: 20.4% – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% - 22.3%), p=0.031.

The analysis of the determinants of fatigue is provided in **Tables 1 and 2**.

Table 1: Bivariate and multivariable analysis of the continuous determinants of fatigue in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2225	623				
Age (years)	61.9 ± 9.8	60.0 ± 9.8	<0.001	-	-	
BMI (kg/m^2)	26.1 ± 4.4	27.4 ± 5.0	<0.001	-	-	
Handgrip (kg)	35.0 ± 12.0	33.8 ± 12.0	0.022	35.0 ± 0.2	35.3 ± 0.3	0.430
Ferritin [mcg/l]	149 [92-229]	139 [83-214]	0.034 §	188 ± 4	185 ± 8	0.732
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 2.9]	0.374 §	2.5 ± 0.1	2.4 ± 0.1	0.332
Free T4 [pmol/l]	16.2 ± 2.5	16.3 ± 2.6	0.190	16.2 ± 0.1	16.4 ± 0.1	0.221

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, quality of life and depression.

Table 2: Bivariate and multivariable analysis of the categorical determinants of fatigue in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable	
	No	**Yes**	**p-value**		**p-value**
Gender			0.031		
Man	1066 (47.9)	268 (43.0)		1 (ref)	
Woman	1159 (52.1)	355 (57.0)		1.25 (0.99 - 1.58)	0.065
Age group			<0.001		
45-54	643 (28.9)	236 (37.9)		1 (ref)	
55-64	724 (32.5)	209 (33.6)		0.69 (0.53 - 0.90)	0.006
64-74	626 (28.1)	113 (18.1)		0.43 (0.31 - 0.59)	<0.001
75+	232 (10.4)	65 (10.4)		0.60 (0.40 - 0.90)	0.013
Educational level			0.017		
Primary	249 (11.2)	93 (14.9)		1 (ref)	
Apprenticeship	794 (35.7)	221 (35.5)		1.05 (0.73 - 1.51)	0.782
High school	626 (28.1)	182 (29.2)		1.13 (0.78 - 1.64)	0.520
University	556 (25.0)	127 (20.4)		0.98 (0.66 - 1.46)	0.937
Smoking categories			0.279		
Never	907 (41.7)	242 (39.7)		-	
Former	866 (39.8)	264 (43.4)		-	
Current	402 (18.5)	103 (16.9)		-	
BMI categories			<0.001		
Underweight	37 (1.7)	5 (0.8)		0.69 (0.24 - 2.01)	0.495
Normal	920 (41.4)	219 (35.2)		1 (ref)	
Overweight	914 (41.1)	243 (39.0)		1.01 (0.78 - 1.31)	0.942
Obese	354 (15.9)	156 (25.0)		1.40 (1.03 - 1.91)	0.032
Insomnia categories			<0.001		
No insomnia	1782 (86.2)	335 (62.6)		1 (ref)	
Subthreshold	233 (11.3)	114 (21.3)		1.57 (1.16 - 2.13)	0.003
Clinical insomnia	53 (2.6)	86 (16.1)		3.76 (2.41 - 5.86)	<0.001
Caffeinated drinks			0.147		
None	205 (9.5)	75 (12.3)		-	
1-3/day	1418 (65.5)	374 (61.5)		-	
4-6/day	471 (21.8)	137 (22.5)		-	
7+/day	70 (3.2)	22 (3.6)		-	
Self-rated health			<0.001		
Very good	621 (27.9)	58 (9.3)		1 (ref)	
Good	1323 (59.5)	294 (47.2)		1.94 (1.39 - 2.71)	<0.001
Average	270 (12.1)	232 (37.2)		5.55 (3.78 - 8.14)	<0.001
Bad + Very bad	11 (0.5)	39 (6.3)		14.1 (5.95 - 33.4)	<0.001
Cardiovascular disease			0.697		
No	2036 (91.5)	567 (91.0)		-	
Yes	189 (8.5)	56 (9.0)		-	
Diabetes			<0.001		
No	2069 (93.2)	547 (87.9)		1 (ref)	
Yes	151 (6.8)	75 (12.1)		1.24 (0.82 - 1.87)	0.306
Depression (CES-D)			<0.001		
No	2026 (93.8)	404 (67.6)		1 (ref)	
Yes	135 (6.3)	194 (32.4)		3.26 (2.38 - 4.46)	<0.001
Anemia			0.008		

No	2151 (96.7)	588 (94.4)		1 (ref)	
Yes	74 (3.3)	35 (5.6)		1.70 (1.00 - 2.89)	0.049
Ferritin categories			0.436		
>50	2016 (90.6)	558 (89.6)		-	
Normal + low	209 (9.4)	65 (10.4)		-	
TSH categories			0.017		
High > 4.22	197 (8.9)	56 (9.0)		1.13 (0.77 - 1.66)	0.533
Normal 0.27-4.22	2015 (90.6)	556 (89.3)		1 (ref)	
Low < 0.27	13 (0.6)	11 (1.8)		2.50 (0.91 - 6.85)	0.075
Free T4 categories			0.651		
High > 22	47 (2.1)	17 (2.7)		-	
Normal 12-22	2122 (95.4)	591 (94.9)		-	
Low < 12	56 (2.5)	15 (2.4)		-	
Anti-hypertensive			0.108		
No	1550 (69.7)	413 (66.3)		-	
Yes	675 (30.3)	210 (33.7)		-	
Anti-histaminics			0.007		
No	2181 (98)	599 (96.2)		1 (ref)	
Yes	44 (2.0)	24 (3.9)		1.30 (0.69 - 2.46)	0.417
Antidepressants			<0.001		
No	2062 (92.7)	508 (81.5)		1 (ref)	
Yes	163 (7.3)	115 (18.5)		1.44 (1.02 - 2.04)	0.040
Hypnotics			<0.001		
No	2146 (96.5)	580 (93.1)		1 (ref)	
Yes	79 (3.6)	43 (6.9)		0.57 (0.32 - 1.03)	0.062

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Only variables with $p<0.05$ in the bivariate analysis were retained for the multivariable analysis.

On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels (**Table 1**). Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression and low TSH values (**Table 2**). Finally, participants with fatigue had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad (**Table 2**).

Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics (**Table 2**).

Sensitivity analysis using inverse probability weighting led to similar findings, except that anaemia and antidepressants were no longer associated with fatigue, while a positive association was found between low TSH levels and fatigue (**Supplemental table 2**).

Discussion

To our knowledge, this is one of the few studies assessing the prevalence and determinants of fatigue in a general population setting, and the first study conducted in Switzerland. Our results indicate that one out of five people aged between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and decreasing self-rated health status were positively associated, while older age was negatively associated with fatigue.

Prevalence of fatigue

Fatigue was present in one out of five participants (22.1%), a finding in agreement with the sole two studies that assessed fatigue in the general population. The study by Loge et al. [6] reported a prevalence of 22% using the Chalder fatigue scale, while the study by Lerdal et al. [16] reported a prevalence of 23.1% using the FSS. Still, the study by Lerdal et al. used a higher cut-off (≥5) to define fatigue, while we used the original threshold (≥4).[21 22] Using a cut-off ≥4, the prevalence of fatigue in the study by Lerdal et al. was 46.7%, which was considered as an overestimation. A study conducted in general practice attendees reported a prevalence of fatigue 38% using the Chalder fatigue scale,[15] and a study conducted in the Danish working population reported a prevalence of fatigue of 22% using

other fatigue measures.[13] Overall, our results suggest that the prevalence of fatigue in the Lausanne population is comparable of even lower than reported previously.

Clinical and societal determinants of fatigue

Women tended to report fatigue more frequently than men, but this association was no longer significant after multivariable adjustment. Higher prevalence of fatigue in women has been found in some studies [6 9] but not in others.[12] In a Swedish study conducted in 2014, Engberg et al. [10] considered that this difference could be due factors related to gender inequalities regarding household responsibilities and child raising, as the gender gap in general fatigue was largest among those aged <55 years.

Younger people reported fatigue more frequently than elderly, a finding in agreement with a Swedish study conducted in 2014.[10] Similarly, in a previous study we found, that older subjects complain less of sleepiness.[27] Conversely, earlier studies (1990-2000) found a positive association between age and fatigue.[6 11 19] A possible explanation for this difference is that older people might have a better quality of life nowadays and are less depressed. Indeed, in our study, the lowest prevalence of fatigue was reported by participants aged 64-74 years, which are the "young" retired with few comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and 12.5% in the 45-54 and 55-64 years, respectively, p-value<0.001).

Obese subjects had a higher prevalence of fatigue, a finding in agreement with studies conducted in the USA [28] and in the UK.[17] Obesity is a risk factor for sleep apnoea, which leads to increased daytime sleepiness. Still, the association persisted after adjusting for insomnia, a finding in agreement with a study that showed that obese subjects have excessive fatigue independently of sleep-disordered breathing.[29] Because it excluded too much subjects, we did not correlate obesity and sleep-disordered breathing in our study. A possible explanation could be the increase in proinflammatory cytokines in obese subjects,[30]

which would lead to higher fatigue,[31] but other factors such as decreased physical fitness should be further explored.

A positive association was found between self-reported clinical insomnia and fatigue, and this association was independent of obesity, depression and antidepressant medication. Fatigue is a core symptom of insomnia [32] and a Norwegian study conducted in 2014 showed that reducing insomnia severity led to a concomitant reduction in fatigue.[33] Interestingly, many subjects with sleep complaints do not consult for this issue,[34] which might lead to an underestimation of its prevalence. Overall, our results suggest that insomnia is an important and underestimated factor of fatigue.

Both depression and antidepressant medication were independently and positively associated with fatigue. The association between depression and fatigue has been repeatedly reported,[17 35-37] and the same applies for antidepressant medication.[2] Our results confirm the known association between depression and fatigue, and suggest that antidepressant treatment might not systematically relief fatigue among depressive subjects.

A strong association was found between poor self-rated health and fatigue, a finding also reported elsewhere.[10 13] Low self-rated health has been associated with increased levels of inflammatory markers such as interleukin 6 and CRP,[38] which in turn could trigger fatigue. Conversely, increased fatigue might lead to a lower rating of oneself health status. Due to the cross-sectional setting of our study, it is not yet possible to ascertain causality, but the ongoing follow-up of the CoLaus participants will provide the answer in the next years.

Biological determinants of fatigue

Participants with anaemia had a higher likelihood of reporting fatigue. This finding is in agreement with the literature,[39 40] although no association between fatigue and low haemoglobin levels was found in an UK study.[17] A possible explanation is that in the UK study, anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds used in our study (<133 g/l for men and <117 g/l for women). This led to a small sample size

(356 participants, corresponding to 1.9% of the overall sample) and thus a low statistical power.

Hypothyroidism is often cited during the investigation of fatigue.[7] In this study participants with low TSH levels reported fatigue more frequently, but his association was significant only after multivariable analysis with inverse probability weighting. Further, the prevalence of low TSH levels was <1% in the overall sample. The associations between hypothyroidism and fatigue have long been controversial.[7] Basu et al. found no association between TSH categories and fatigue [17] and Canaris et al [41] reported that the association between fatigue and hypothyroidism was weak. Overall, our results suggest that, in presence of fatigue, hypothyroidism is an unlikely cause and should not be systematically assessed.

Implications for clinical practice

A previous paper [2] suggested a list of items to explore in presence of a patient with fatigue. Based on our study findings, we propose to update and to rank the conditions to explore. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea (namely in presence of a patient with obesity) should be assessed first, followed by depression. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step. Sleep complaints and fatigue in older subjects are not a part of aging and should prompt the identification of underlying cause.

Regarding management of fatigue, lifestyle measures to improve sleep quality and quantity should be preferred to medication.[42] In case of depression, it will be important to warn patient that antidepressor medication might not necessarily lead into rapid relief of fatigue. Finally, non-drug interventions on stress management and health promotion like relaxation, time management, cognitive reframing could improve self-rated health [43] and so reduce fatigue.

Strengths and limitations

This study has several strengths. Firstly, it is one of the few studies assessing the prevalence and the determinants of fatigue in a population-based sample, which is of interest for public health. Secondly, the age group considered corresponds to most of the patients in general clinical practice, so the findings are also of interests for general practitioners and internists. Finally, it explored a large panel of possible determinants of fatigue, thus allowing the identification of factors significantly and independently associated with fatigue.

This study has also several limitations. Firstly, its cross sectional setting precludes the identification of the causes of fatigue, as reverse causality is possible (i.e. fatigue leading to depression and vice-versa).[2] All participants of the CoLaus study are currently being re-contacted and re-examined, so that a prospective analysis of the causes of fatigue will be feasible within two years. Secondly, only the German version of the FSS has been validated in Switzerland; the French version used in this study has not yet been validated. Hence, it is possible that the true prevalence levels of fatigue might be under- or over-estimated. Still, our results provide a first estimation of the prevalence of fatigue in the general population, which could serve as a reference for further studies. Finally, the study was limited to subjects aged 45 to 86, and no information was collected among younger subjects, where prevalence of fatigue might be higher due to parental and professional duties.[44]

Conclusion

In a population-based sample, fatigue was present in one out of five subjects aged 45 to 86. The major determinants of fatigue were obesity, insomnia, depression, anaemia and antidepressant medication.

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COMPETING INTERESTS

The authors report no competing interests.

AUTHORS' CONTRIBUTION

CG-D made the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and wrote part of the manuscript. PV conceived the study and revised the manuscript for important intellectual content. PM-V has full access to the data and is the guarantor of the manuscript. All authors have read and approved this version of the manuscript.

PATIENT CONSENT FORM

Not applicable

DATA SHARING STATEMENT

Non-identifiable individual-level data are available for researchers who seek to answer questions related to health and disease in the context of research projects who meet the criteria for data sharing by research committees. Please follow the instructions at https://www.colaus-psycolaus.ch/ for information on how to submit an application for gaining access to CoLaus data.

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Not applicable.

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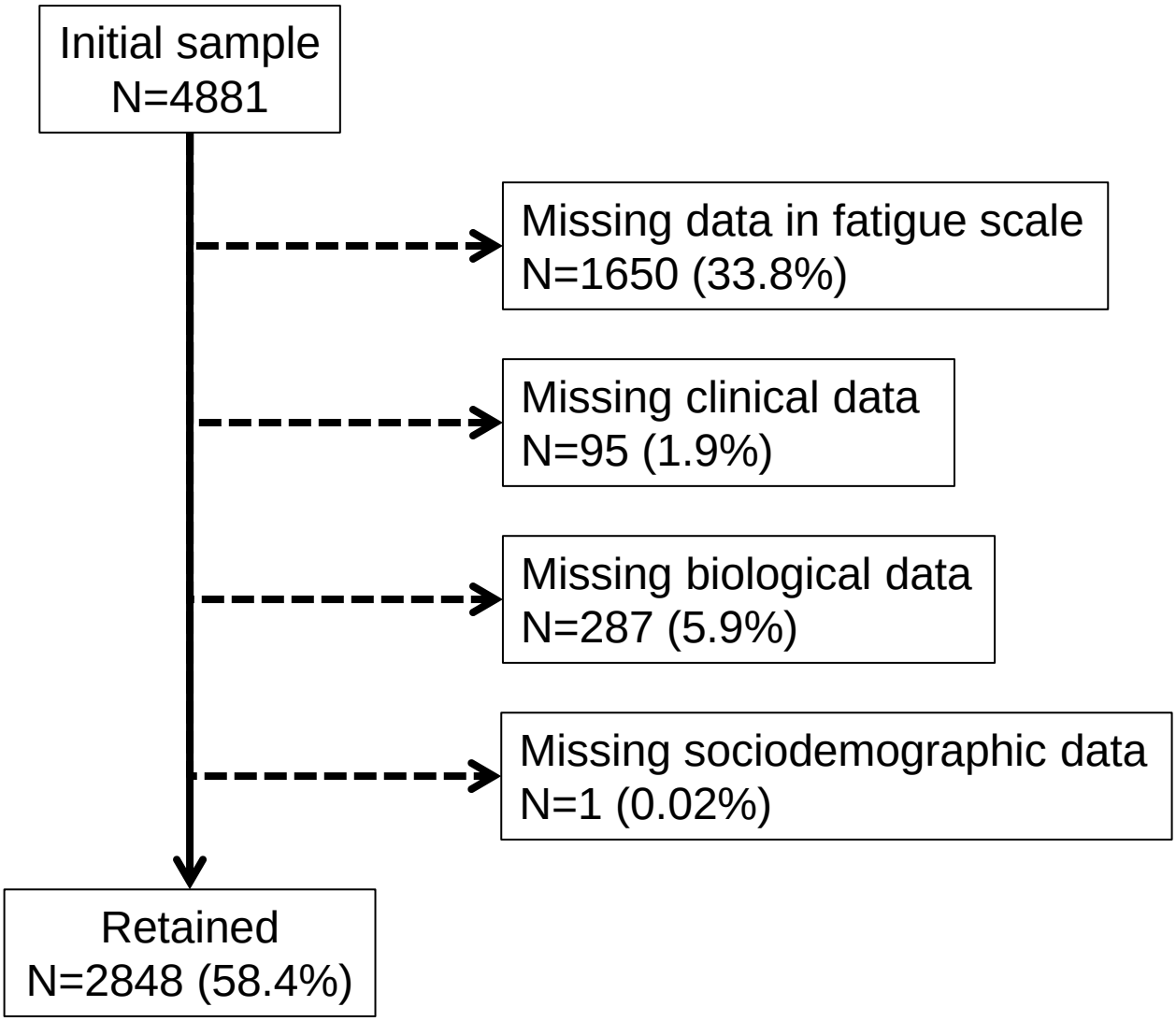
Supplemental figure 1: The reasons for exclusion



Exclusion if missing data in fatigue scale, missing clinical, biological and sociodemographic data

Supplemental table 1: comparison between excluded and included participants

	Included	Excluded	p-value
N	2848	2033	
Woman (%)	1514 (53.2)	1175 (57.8)	0.001
Age (years)	61.5 ± 9.8	65.0 ± 11.0	<0.001
Age groups			<0.001
45-54	879 (30.9)	467 (23.0)	
55-64	933 (32.8)	569 (28.0)	
64-74	739 (26.0)	560 (27.6)	
75+	297 (10.4)	437 (21.5)	
Educational level			<0.001
University	683 (24.0)	348 (17.2)	
High school	808 (28.4)	450 (22.2)	
Apprenticeship	1015 (35.6)	734 (36.2)	
Primary	342 (12.0)	497 (24.5)	
Smoking categories			0.015
Never	1149 (41.3)	737 (43.1)	
Former	1130 (40.6)	624 (36.5)	
Current	505 (18.1)	350 (20.5)	
BMI (kg/m^2)	26.4 ± 4.5	26.5 ± 5.0	0.525
BMI categories			0.038
Underweight	42 (1.5)	33 (2.0)	
Normal	1139 (40.0)	643 (39.4)	
Overweight	1157 (40.6)	618 (37.8)	
Obese	510 (17.9)	339 (20.8)	
Caffeinated drinks			<0.001
None	280 (10.1)	182 (11.3)	
1-3/day	1792 (64.7)	1108 (69.0)	
4-6/day	608 (21.9)	272 (16.9)	
7+/day	92 (3.3)	44 (2.7)	
Self-rated health			<0.001
Very good	679 (23.8)	353 (17.8)	
Good	1617 (56.8)	1094 (55.2)	
Average	502 (17.6)	464 (23.4)	
Bad + Very bad	50 (1.8)	72 (3.6)	
Cardiovascular disease	245 (8.6)	274 (13.5)	<0.001
Diabetes	226 (8.0)	256 (15.0)	<0.001
Depression	329 (11.9)	93 (11.9)	0.971
Anemia	109 (3.8)	108 (6.5)	<0.001
Ferritin [mcg/l]	227 [147 - 2.97]	220 [141 - 2.93]	0.058
TSH [mUI/l]	3.0 [2.1 - 3.0]	3.0 [2.1 - 2.9]	0.375
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 3.3	0.534
Anti-hypertensive drugs	885 (31.1)	812 (39.9)	<0.001
Anti-histaminics	68 (2.4)	32 (1.6)	0.048
Antidepressants	278 (9.8)	246 (12.1)	0.009
Hypnotics	122 (4.3)	145 (7.1)	<0.001

BMI, body mass index. Results are expressed as number of participants (column percentage) for categorical variables and as average±standard deviation or median [interquartile range] for continuous variables. Between-group comparison performed using chi-square for categorical variables and using student's t-test or Kruskal-Wallis test (§) for continuous variables.

Supplemental table 2: Multivariable analysis of the categorical determinants of fatigue in the CoLaus study, Lausanne, Switzerland, 2014-2017, using inverse probability weighting.

	Odds ratio (95% CI)	P-value
Gender (woman vs. man)	1.26 (0.99 - 1.61)	0.064
Age group		
45-54	1 (ref)	
55-64	0.70 (0.53 - 0.91)	0.009
64-74	0.43 (0.31 - 0.59)	<0.001
75+	0.64 (0.42 - 0.96)	0.031
Educational level		
Primary	1 (ref)	
Apprenticeship	1.02 (0.70 - 1.48)	0.923
High school	1.08 (0.74 - 1.59)	0.678
University	0.94 (0.63 - 1.41)	0.768
BMI categories		
Underweight	0.71 (0.20 - 2.56)	0.598
Normal	1 (ref)	
Overweight	1.03 (0.79 - 1.34)	0.833
Obese	1.44 (1.05 - 1.98)	0.022
Insomnia categories		
No insomnia	1 (ref)	
Subthreshold	1.57 (1.15 - 2.14)	0.004
Clinical insomnia	3.74 (2.29 - 6.10)	<0.001
Self-rated health		
Very good	1 (ref)	
Good	1.92 (1.37 - 2.69)	<0.001
Average	5.51 (3.71 - 8.17)	<0.001
Bad + Very bad	17.2 (7.51 - 39.3)	<0.001
Diabetes (yes vs. no)	1.15 (0.76 - 1.74)	0.501
Depression (CES-D, yes vs. no)	3.21 (2.34 - 4.42)	<0.001
Anemia (yes vs. no)	1.58 (0.91 - 2.76)	0.107
TSH categories		
High > 4.22	1.15 (0.77 - 1.70)	0.499
Normal 0.27-4.22	1 (ref)	
Low < 0.27	3.30 (1.09 - 10.0)	0.035
Anti-histaminics (yes vs. no)	1.33 (0.69 - 2.57)	0.398
Antidepressants (yes vs. no)	1.39 (0.98 - 1.97)	0.069
Hypnotics (yes vs. no)	0.59 (0.31 - 1.10)	0.098

Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Multivariable analysis performed using logistic regression with inverse probability weighting.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and factors associated with fatigue in the Lausanne middle-aged population: A population based cross-sectional survey

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Abstract

Objective: To assess the prevalence and factors associated with fatigue in the general population.

Design: Population based cross-sectional survey performed between May 2014 and April 2017.

Setting: General population of the city of Lausanne, Switzerland.

Participants: 2848 participants (53.2% women, age range 45-86 years).

Primary outcome measure: Prevalence of fatigue the previous week, defined as a score ≥4 using the Fatigue Severity Scale (FSS).

Results: The prevalence of fatigue was 21.9% (95% CI: 20.4% – 23.4%) in the total sample. On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels. Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression, low TSH values, had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad. Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated with fatigue; while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics.

Conclusion: In a population-based sample aged 45 to 86, fatigue was present in one out of five subjects. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea should be assessed first, followed by depression. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step. Sleep complaints and fatigue in older subjects are not due to aging and should prompt the identification of the underlying cause.

Keywords: fatigue; prevalence; epidemiology; Fatigue severity scale

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study assessed the prevalence and factors associated with fatigue in a general population setting.
- A large panel of associated with fatigue was evaluated.
- A list of the most frequent determinants was established, facilitating etiological search in clinical practice
- The study was limited to subjects aged 45 to 86, so results do not apply to younger or older groups.

INTRODUCTION

Fatigue is usually defined as "an unpleasant physical, cognitive and emotional symptom described as a tiredness not relieved by common strategies that restore energy".[1] Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities. [1] Indeed, fatigue is a common symptom with prevalence rates varying between 4 and 45%. [2-4] This ten-fold range in prevalence rates is likely due to the different settings (i.e. general practice [5] or workers [6]) or the different methods used to assess fatigue. [7]

In healthy subjects, tiredness or sleepiness are a natural occurrence after physical or mental efforts, and are usually relieved by rest. [8 9] While fatigue is defined as extreme and persistent tiredness, weakness or exhaustion, of mental and/or physical origin [7] that is not relieved by rest. Fatigue is defined in duration as recent (<1 month) prolonged (1 to 6 months) and chronic (>6 months) [10]. When unexplained, chronic fatigue can be considered either as a syndrome (characterized by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches) [11] or as idiopathic (absence of other symptoms).

Fatigue is one of the most common complaints reported in primary care [12] and is associated with a decreased quality of life and increased morbidity and mortality in the general population. [13] Fatigue is a multidimensional concept, and several determinants have been proposed. Although a cause (somatic or psychiatric) is identifiable in 2/3 of fatigue cases, 1/3 of fatigue cases still have no specific diagnosis.[10] The most frequent diagnoses associated with fatigue are viral or upper respiratory tract infection, iron deficiency anemia, adverse effects of medication, depression or other mental disorders.[14] Fatigue has also been associated with female sex, [8 15] older age [16 17] and lower socioeconomic status, [16 17] although the association with the last two determinants were not found in some studies. [8 18] Importantly, most studies on fatigue have been conducted in selected populations such as workers [6] or general practice attendees.[2 5 18] To our knowledge, only two studies have assessed the prevalence of fatigue in the general population [8 19] and only a few have explored the

determinants of fatigue in the general population.[13 15-17 20 21] Furthermore, most studies focused on socio-economic and disease determinants of fatigue, while information regarding the biological determinants (i.e. anemia or thyroid pathology) [13] or the medications associated with fatigue is scarce. Moreover, to date, little is known about the prevalence of fatigue and its determinants in Switzerland.

Hence, this study aimed to examine the prevalence and the factors associated with fatigue in a population-based sample from the city of Lausanne, Switzerland.

POPULATION AND METHODS

Study population

The CoLaus study is a population-based cohort exploring biological, genetic, and environmental determinants of cardiovascular diseases. Detailed descriptions of the study design have been reported elsewhere.[22] Briefly, a non-stratified random representative sample of the population of Lausanne was recruited between 2003 and 2006 using the following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate. The first follow-up was performed between April 2009 and September 2012 and the second follow-up between May 2014 and April 2017. At both baseline and subsequent follow-ups, participants were invited to attend a clinical examination at the Lausanne university hospital. Participants received a paper questionnaire at home, which they filled prior to the clinical examination. During the clinical examination, a second questionnaire regarding personal and family history of cardiovascular disease and cardiovascular risk factors was applied. For more details, please consult www.colaus-psycolaus.ch.

As fatigue was only assessed in the second follow-up, data from the second follow-up, which included 4881 of the initial 6773 participants recruited at baseline, was used. At the second follow-up, participants were aged 45-86 years.

Fatigue scale

Fatigue severity during the previous week was assessed by the 9 items Fatigue Severity Scale (FSS). [9] The FSS is one of the most commonly used fatigue questionnaires. It had been validated in a healthy population setting in German-speaking Switzerland [23], Portugal [24] and Norway [19]. It is a simple, time-saving, self-administrated questionnaire allowing its use in large epidemiological studies and has a high test-retest reliability. [7] The questionnaire is composed of nine questions; responses are graded using a Likert scale from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement. The final score is the mean value of the nine responses, and a score ≥4 is considered as having severe fatigue. This cutoff was initially proposed because <5% of healthy controls rate their fatigue at that level, whereas 60-90% of patients with medical disorders experience fatigue at or above this level. [9] An example of the questionnaire (in French) is provided in **Annex 1**. To our knowledge, the French version of the FSS has not yet been validated in Switzerland. Still, the Cronbach's alpha for the questionnaire was 0.918, suggesting an excellent internal consistency.

Covariates

Socioeconomic and lifestyle variables were collected using a self-administered questionnaire. Smoking status was categorized into never, former and current smoker. Educational level was collected at baseline and categorized as obligatory school, apprenticeship, high school/college or university.

Insomnia was assessed using the Insomnia Severity Index (ISI).[25] The questionnaire has 16 items evaluating the nature, severity, and impact of insomnia over the last month; namely difficulties falling asleep, sleep maintenance problems, and early morning awakening, sleep dissatisfaction, interference of sleep disturbances with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Responses range from 0 "Not at all" to 4 "Extremely". Items were scaled 0-4 and then summed to obtain the global ISI score (range: 0-28). The questionnaire is provided in **Annex 2**. Clinically significant insomnia was defined as an ISI score ≥15 (moderate to severe intensity).[25]

Depression was assessed with the CES-D [26], a 20 item self-report instrument, developed for research in the general population, that is used to assess the severity of depressive symptoms over the past week on a 4-point scale. It was translated into French by Fuhrer and Rouillon.[27] It has been used in other recent epidemiological studies assessing the link between depression and cardiovascular risk factors [28]. The questionnaire is composed of 20 questions; responses are graded from 0 to 3, where 0 indicates rarely or never (less than one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the 20 responses (possible range is 0-60), and a score ≥16 is considered as a risk for depression.

Self-rated health was assessed by a single question where participants had to rate their current health status from five categories ranging from “very bad” to “very good”. As the number of participants rating their health as “very bad” was very small, they were grouped with the participants who rated their health as “bad”.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight/height^2 and categorized as underweight (BMI<18.5 kg/m^2), normal (18.5≤BMI<25 kg/m^2); overweight (25≤ BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2).

Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and 30° of dorsiflexion. Three measurements were performed consecutively with the right hand and the highest value (expressed in kg) was included in the analyses.

Caffeinated drink consumption was assessed by the question “How many cups or cans of drinks containing caffeine (coffee, tea, coke or similar) do you drink per day?” with possible answers “None”, “1-3”, “4-6” and “7 or more”.

Participants were asked to report all medications (prescribed or bought over the counter) they took during the last 6 months. Medications were coded using the Anatomical, Therapeutic Chemical (ATC) classification of the world health organization (www.whocc.no/atc_ddd_index/). Antihistamics were defined as any ATC code beginning with "R06"; antidepressants were defined as an ATC code beginning with "N05BD" or N06AA" or "N06AB" or "N06AF" or "N06AG" or "N06AX" or "N06CA"; hypnotics were defined as any ATC code beginning with "N05C". Antihypertensive drugs were defined by asking the participants if they were taking drugs for hypertension.

Diabetes was defined by a fasting plasma glucose ≥7 mmol/L and/or the presence of an antidiabetic drug treatment (oral or insulin). Personal history of cardio vascular disease was assessed by asking the participant if he/she had sustained a coronary event (myocardial infarction or angina pectoris) or a stroke.

Biological assays were performed by the CHUV Clinical Laboratory on fresh blood samples within 2 hours of blood collection, and additional aliquots were stored at –80°C. All measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland). The following analytical procedures (with maximum inter and intra-batch CVs) were used: high sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by immunoturbidimetric method (Tina-quant 4th generation, Roche Diagnostics, Switzerland) with a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid stimulating hormone (TSH) and free T_4 were assessed by chemiluminescence (ECLIA) on a Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free T_4.

Exclusion criteria

Participants were excluded if they lacked 1) any answer to the fatigue questionnaire; 2) clinical data such as age, body mass index, smoking, depression, insomnia or medications;

3) biological measures such as haemoglobin or thyroid hormones and 4) socioeconomic data such as educational level.

Ethical statement and consent

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-up. The full decisions of the CER-VD can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Patient and Public Involvement

No patients or public were involved in this study design, conduct or analysis.

Statistical analysis

Statistical analysis was performed using Stata version 15.1 for windows (Stata Corp, College Station, Texas, USA). Prevalence rates for fatigue were expressed as percentage and 95% confidence interval (CI). Descriptive results were expressed as number of participants (percentage) for categorical variables or as average±standard deviation for continuous variables. Bivariate analyses were performed using chi-square or Fisher's exact test for categorical variables and student's t-test or Kruskal-Wallis test for continuous variables. All categorical variables significantly ($p<0.05$) associated with fatigue in the bivariate analysis were included in the multivariable analysis. Multivariable analysis was performed using analysis of variance or logistic regression with fatigue (dichotomized into yes/no) as dependent variable; results were expressed as multivariable-adjusted mean±standard error for continuous variables or as Odds ratio (OR) and 95% CI for categorical variables.

Sensitivity analyses were conducted using a FSS threshold of 5. Further, as the number of excluded participants was high, other sensitivity analyses were conducted by creating a propensity score for being excluded [29]. The propensity score was computed using

logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly associated with exclusion as independent variables. A probability of exclusion was computed for each participant, and the inverse of the probability was used for weighting.

Statistical significance was assessed for a two-sided test with $p<0.05$.

Results

Study population

Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most frequent reason was lack of data regarding fatigue. The comparison between included and excluded participants is provided in **supplemental table 1** and the results of the multivariable analysis are provided in **supplemental table 2**. Excluded participants were more frequently women, were older, had a lower educational level, were more frequently never or current smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and hypertension) and rated their health worse.

Prevalence and factors associated with fatigue

The overall prevalence of fatigue as defined by a FSS ≥4 was 21.9% (95% CI: 20.4% – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% - 22.3%), p=0.031. The distribution of the FSS ≥5 (prevalence of fatigue 10.9%) is provided in **supplemental figure 2**; the number of participants with fatigue decreased when the levels of FSS increased.

The analysis of the factors associated with fatigue as defined by a FSS ≥4 is provided in **Tables 1 and 2**.

Table 1: Bivariate and multivariable analysis of the continuous factors associated with fatigue as defined by a Fatigue Severity Scale ≥4 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2225	623				
Age (years)	61.9 ± 9.8	60.0 ± 9.8	<0.001	-	-	
BMI (kg/m^2)	26.1 ± 4.4	27.4 ± 5.0	<0.001	-	-	
Handgrip (kg)	35.0 ± 12.0	33.8 ± 12.0	0.022	35.0 ± 0.2	35.3 ± 0.3	0.430
Ferritin [mcg/l]	149 [92-229]	139 [83-214]	0.034 §	188 ± 4	185 ± 8	0.732
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 2.9]	0.374 §	2.5 ± 0.1	2.4 ± 0.1	0.332
Free T4 [pmol/l]	16.2 ± 2.5	16.3 ± 2.6	0.190	16.2 ± 0.1	16.4 ± 0.1	0.221

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, self-rated health and depression.

Table 2: Bivariate and multivariable analysis of the categorical factors associated with fatigue as defined by a Fatigue Severity Scale ≥4 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable	
	No fatigue	**Fatigue**	**p-value**	**OR (95% CI)**	**p-value**
Gender			0.031		
Man	1066 (47.9)	268 (43.0)		1 (ref)	
Woman	1159 (52.1)	355 (57.0)		1.25 (0.99 - 1.58)	0.065
Age group			<0.001		
45-54	643 (28.9)	236 (37.9)		1 (ref)	
55-64	724 (32.5)	209 (33.6)		0.69 (0.53 - 0.90)	0.006
64-74	626 (28.1)	113 (18.1)		0.43 (0.31 - 0.59)	<0.001
75+	232 (10.4)	65 (10.4)		0.60 (0.40 - 0.90)	0.013
Educational level			0.017		
Primary	249 (11.2)	93 (14.9)		1 (ref)	
Apprenticeship	794 (35.7)	221 (35.5)		1.05 (0.73 - 1.51)	0.782
High school	626 (28.1)	182 (29.2)		1.13 (0.78 - 1.64)	0.520
University	556 (25.0)	127 (20.4)		0.98 (0.66 - 1.46)	0.937
Smoking categories			0.279		
Never	907 (41.7)	242 (39.7)		-	
Former	866 (39.8)	264 (43.4)		-	
Current	402 (18.5)	103 (16.9)		-	
BMI categories			<0.001		
Underweight	37 (1.7)	5 (0.8)		0.69 (0.24 - 2.01)	0.495
Normal	920 (41.4)	219 (35.2)		1 (ref)	
Overweight	914 (41.1)	243 (39.0)		1.01 (0.78 - 1.31)	0.942
Obese	354 (15.9)	156 (25.0)		1.40 (1.03 - 1.91)	0.032
Insomnia categories			<0.001		
No insomnia	1782 (86.2)	335 (62.6)		1 (ref)	
Subthreshold	233 (11.3)	114 (21.3)		1.57 (1.16 - 2.13)	0.003
Clinical insomnia	53 (2.6)	86 (16.1)		3.76 (2.41 - 5.86)	<0.001
Caffeinated drinks			0.147		
None	205 (9.5)	75 (12.3)		-	
1-3/day	1418 (65.5)	374 (61.5)		-	
4-6/day	471 (21.8)	137 (22.5)		-	
7+/day	70 (3.2)	22 (3.6)		-	
Self-rated health			<0.001		
Very good	621 (27.9)	58 (9.3)		1 (ref)	
Good	1323 (59.5)	294 (47.2)		1.94 (1.39 - 2.71)	<0.001
Average	270 (12.1)	232 (37.2)		5.55 (3.78 - 8.14)	<0.001
Bad + Very bad	11 (0.5)	39 (6.3)		14.1 (5.95 - 33.4)	<0.001
Cardiovascular disease			0.697		
No	2036 (91.5)	567 (91.0)		-	
Yes	189 (8.5)	56 (9.0)		-	
Diabetes			<0.001		
No	2069 (93.2)	547 (87.9)		1 (ref)	
Yes	151 (6.8)	75 (12.1)		1.24 (0.82 - 1.87)	0.306
Depression (CES-D)			<0.001		
No	2026 (93.8)	404 (67.6)		1 (ref)	
Yes	135 (6.3)	194 (32.4)		3.26 (2.38 - 4.46)	<0.001
Anemia			0.008		
No	2151 (96.7)	588 (94.4)		1 (ref)	

Yes	74 (3.3)	35 (5.6)		1.70 (1.00 - 2.89)	0.049
Ferritin categories			0.436		
>50	2016 (90.6)	558 (89.6)		-	
Normal + low	209 (9.4)	65 (10.4)		-	
TSH categories			0.017		
High > 4.22	197 (8.9)	56 (9.0)		1.13 (0.77 - 1.66)	0.533
Normal 0.27-4.22	2015 (90.6)	556 (89.3)		1 (ref)	
Low < 0.27	13 (0.6)	11 (1.8)		2.50 (0.91 - 6.85)	0.075
Free T4 categories			0.651		
High > 22	47 (2.1)	17 (2.7)		-	
Normal 12-22	2122 (95.4)	591 (94.9)		-	
Low < 12	56 (2.5)	15 (2.4)		-	
Anti-hypertensive			0.108		
No	1550 (69.7)	413 (66.3)		-	
Yes	675 (30.3)	210 (33.7)		-	
Anti-histaminics			0.007		
No	2181 (98)	599 (96.2)		1 (ref)	
Yes	44 (2.0)	24 (3.9)		1.30 (0.69 - 2.46)	0.417
Antidepressants			<0.001		
No	2062 (92.7)	508 (81.5)		1 (ref)	
Yes	163 (7.3)	115 (18.5)		1.44 (1.02 - 2.04)	0.040
Hypnotics			<0.001		
No	2146 (96.5)	580 (93.1)		1 (ref)	
Yes	79 (3.6)	43 (6.9)		0.57 (0.32 - 1.03)	0.062

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Only variables with p<0.05 in the bivariate analysis were retained for the multivariable analysis.

On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels (**Table 1**). Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression and low TSH values (**Table 2**). Finally, participants with fatigue had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad (**Table 2**).

Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26

(2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics (**Table 2**).

Sensitivity analyses

The overall prevalence of fatigue as defined by a FSS ≥5 was 10.9% (95% CI: 9.7% – 12.1%) and was higher in women 12.3% (10.7% - 14.0%) than in men 9.3% (7.8% - 11.1%), p=0.011. The results of the sensitivity analyses using a FSS threshold of ≥5 are provided in **supplemental tables 3 and 4**. Overall, the results were comparable with those using a threshold of ≥4: gender, insomnia categories (p-value for trend <0.001), and low self-rated health status (p-value for trend <0.001) were positively associated with fatigue. Conversely, no association was found for age, obesity, diabetes, TSH levels, antihistaminics, antidepressives or hypnotics (**supplemental table 4**).

Sensitivity analysis using inverse probability weighting by the propensity score led to similar findings, except that anemia and antidepressants were no longer associated with fatigue, while a positive association was found between low TSH levels and fatigue (**Supplemental table 5**).

Discussion

To our knowledge, this is one of the few studies assessing the prevalence and the factors associated with fatigue in a general population setting, and the first study conducted in Switzerland. Using a FSS cut-off ≥4, our results indicate that one out of five people aged between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and decreasing self-rated health status were positively associated with fatigue; while older age was negatively associated with fatigue.

Prevalence of fatigue

Using the cut-off of ≥4, fatigue was present in one out of five participants (22.1%), a finding in agreement with the study by Loge et al. [8], which reported a prevalence of 22% among 2323 participants using the Chalder fatigue scale. Conversely, the cross-sectional study by Lerdal et al. [19], which used the FSS in a sample of 1893 participants, reported a prevalence of fatigue of 46.7% and 23.1% using a cut-off of ≥4 and ≥5 respectively, in comparison 22.1% and 10.9% in our study). A study conducted in general practice reported a prevalence of fatigue of 38% using the Chalder fatigue scale,[2] whereas a study conducted in the Dutch working population reported a prevalence of fatigue of 22% using other fatigue measures. [6] Overall, our results suggest that the prevalence of fatigue in the Lausanne population is comparable or lower than reported previously, although the use of different scales to assess fatigue complicates comparison between studies.

Clinical and societal factors associated with fatigue

Women tended to report fatigue more frequently than men, but this association was no longer significant after multivariable adjustment. Higher prevalence of fatigue in women has been found in some studies [8 15] but not in others.[18] In a Swedish study conducted in 2014, Engberg et al. [16] considered that this difference could be due to factors related to gender inequalities regarding household responsibilities and child raising, as the gender gap in general fatigue was largest among those aged <55 years.

Younger people reported fatigue more frequently than elderly, a finding in agreement with a Swedish study conducted in 2014. [16] Similarly, a previous study found that older subjects complain less of sleepiness. [30] Still, this association was no longer statistically significant when the cut off of ≥5 was applied to define fatigue, suggesting that young subjects tend to present with borderline fatigue as suggested previously [19]. Conversely, earlier studies (1990-2000) found a positive association between age and fatigue.[8 17 21] A possible explanation for this difference is that older people might have a better quality of life nowadays and are less depressed. Although there is little information regarding trends in quality of life

among Swiss elderly, the VLV study [31] concluded that quality of life among Swiss elderly increased in the last 30 years [32]. Indeed, in our study, the lowest prevalence of fatigue was reported by participants aged 64-74 years, which are the "young" retired with few comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and 12.5% in the 45-54 and 55-64 years, respectively, p-value<0.001).

Obese subjects had a higher prevalence of fatigue defined by a FSS ≥4. This finding is in agreement with studies conducted in the USA [33] and in the UK.[13] . Still, this association was no longer statistically significant when the cut off of ≥5 was applied to define fatigue, suggesting that obese subjects tend to present with borderline fatigue as suggested previously [19]. Obesity is a risk factor for sleep apnoea, which leads to increased daytime sleepiness. Still, the association persisted after adjusting for insomnia, a finding in agreement with a previous study that showed that obese subjects have excessive fatigue independently of sleep-disordered breathing.[34] Because it excluded too much subjects, we did not correlate obesity and sleep-disordered breathing in our study. A possible explanation could be the increase in proinflammatory cytokines in obese subjects,[35] which would lead to higher fatigue,[36] but other factors such as decreased physical fitness should be further explored.

A positive association was found between self-reported clinical insomnia and fatigue, and this association was independent of obesity, depression and antidepressant medication. Fatigue is a core symptom of insomnia [34] and a Norwegian study conducted in 2014 showed that reducing insomnia severity led to a concomitant reduction in fatigue.[37] Interestingly, many subjects with sleep complaints do not consult for this issue,[38] which might lead to an underestimation of its prevalence. Overall, our results suggest that insomnia is an important and underestimated factor of fatigue.

Both depression and antidepressant medication were independently and positively associated with fatigue. The association between depression and fatigue has been repeatedly reported,[13 39-41] and the same applies for antidepressant medication.[3] Our

results confirm the known association between depression and fatigue, and suggest that antidepressant treatment might not systematically relieve fatigue among depressive subjects. Furthermore, fatigue is a common side effect of antidepressant therapy and a symptom of depression, making the identification of the cause of fatigue difficult with a possibility of reverse causality (fatigue leading to depression and vice versa). We used a one-dimensional tool to evaluate fatigue (FSS); hence, we cannot distinguish between physical and mental fatigue. There is considerable overlap in phenomenology of fatigue and depression or anxiety but there are some important differences. People with fatigue without psychiatric symptoms tend to attribute their symptoms to external causes. Conversely, most depressed people experience self-blame or lowered self-esteem [42]. Further, fatigue and depression commonly appear together. A study conducted in 2009 by Harvey et al. [43], showed that 7% of fatigued persons have no psychiatric symptoms, but remained at increased risk of later psychiatric disorder independently of the severity of fatigue.

A strong association was found between poor self-rated health and fatigue, a finding also reported elsewhere.[6 16] Low self-rated health has been associated with increased levels of inflammatory markers such as interleukin 6 and CRP,[44] which in turn could trigger fatigue. Conversely, increased fatigue might lead to a lower rating of health status.

Biological factors associated with fatigue

Participants with anemia had a higher likelihood of reporting fatigue. This finding is in agreement with the literature,[45 46] although no association between fatigue and low haemoglobin levels was found in a UK study. [13] A possible explanation is that in the UK study, anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds used in our study (<133 g/l for men and <117 g/l for women). This led to a small sample size (356 participants, corresponding to 1.9% of the overall sample) and thus a low statistical power.

Hypothyroidism is often cited during the investigation of fatigue.[10] In this study participants with low TSH levels reported fatigue more frequently, but this association was

significant only after multivariable analysis with inverse probability weighting. Furthermore, the prevalence of low TSH levels was <1% in the overall sample. The associations between hypothyroidism and fatigue have been controversial for a long time.[10] Basu et al. found no association between TSH categories and fatigue [13] and Canaris et al [47] reported that the association between fatigue and hypothyroidism was weak. Overall, our results suggest that, in presence of fatigue, hypothyroidism is an unlikely cause and should not be systematically assessed.

Implications of the study

Based on our study findings, we propose to focus on specific clinical and biological factors amenable to treatment at an individual level. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea (namely in presence of a patient with obesity) and the presence of depression should be assessed. Hence, lifestyle measures to improve sleep quality and quantity should be preferred to medication.[22] In the case of depression, it will be important to warn patients that antidepressor medication might not necessarily lead into rapid relief of fatigue. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step.

At the population level, preventive measures such as stress management and health promotion like relaxation, time management and cognitive reframing (for example within the work environment) could improve sleep quality, increase self-rated health {Hasson, 2005 #615} and consequently reduce fatigue.

Recommendations for future studies

Future studies on the prevalence of fatigue in the general population should focus on the following topics: 1) validate the questionnaires in the population of interest; 2) whenever possible, use a standardised questionnaire to allow comparison between studies.

While some factors such as obesity [13 33], depression [13 39-41] and antidepressor medications [3] were consistently associated with fatigue in our study and in the literature,

controversial findings such as the association between fatigue and gender, age groups and anemia should be further explored.

Strengths and limitations

This study has several strengths. Firstly, it is one of the few studies assessing the prevalence and the factors associated with fatigue in a population-based sample, which is of interest for public health. Secondly, it explored a large panel of possible factors associated with fatigue, thus allowing the identification of factors significantly and independently associated with fatigue.

This study has also several limitations. Firstly, its cross sectional setting precludes the identification of the causes of fatigue, as reverse causality is possible (i.e. fatigue leading to depression and vice-versa).[3] All participants of the CoLaus study are currently being re-contacted and re-examined, so a prospective analysis of the causes of fatigue will be feasible within two years. Secondly, there is no gold standard for the evaluation of fatigue and no official definition of fatigue. Hence, results might vary according to the scale applied or how participants interpret the term “fatigue”. In this study, we chose to use a scale that was previously applied by other authors to facilitate comparisons. Thirdly, only the German version of the FSS has been validated in Switzerland; the French version used in this study has not yet been validated. Hence, it is possible that the true prevalence levels of fatigue might be under- or over-estimated, or that some items of the questionnaire might not be informative. Still, the Cronbach’s alpha for the questionnaire was 0.918, suggesting an excellent internal consistency. Furthermore, our results provide a first estimation of the prevalence of fatigue in the Swiss French-speaking general population, which could serve as a reference for further studies. Fourthly a sizable fraction of the sample was excluded, both between the baseline and the second follow-up, and within the current study, which might limit the generalizability of the findings. For instance, excluded participants were more frequently women; as women reported more frequently fatigue, this might lead to an underestimation of prevalence rates or a decrease in the strength of the associations. Still, an analysis using a propensity score

weighting for the probability of being excluded led to similar findings. Conversely, it was not possible to assess the reasons why participants did not complete the questionnaire. Fifthly, no information was available regarding shift work or the presence of very young children. Still, as a sizable fraction (almost 70%) of the sample was aged over 55 and over 36% of the sample was aged over 64, it is likely that the number of participants either on shift work or with very young children would be small. Sixthly, the FSS explored fatigue during the previous week while the ISI score explored the sleep during the previous month. Hence, it is possible that the time association between the two variables might not be optimal. Still, as the FSS lies within the period encompassed by the ISI, we believe that the associations obtained are clinically relevant. Seventhly, the study is limited to the population of aged 45 to 86, and its generalizability remains to be assessed. For instance, no information was collected regarding other confounders among younger subjects, where prevalence of fatigue might be higher due to parental and professional duties.[48]. Finally, possible biases related to the self-reporting of fatigue could not be avoided, such as over- or under-estimation of symptoms or misunderstanding of what the term “fatigue” meant; still, this dilution bias would lead to a decrease in the strength of the associations, and it would be too restrictive in our opinion to provide a definition of the term “fatigue” to the participants, as different interpretations of the definition itself could also occur.

CONCLUSION

In a population-based sample, fatigue was present in one out of five subjects aged 45 to 86. The major factors associated with fatigue were obesity, insomnia, depression, anemia and antidepressant medication. The results should be interpreted taking into account the high exclusion rate.

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COMPETING INTERESTS

The authors report no competing interests.

AUTHORS' CONTRIBUTION

CG-D conducted the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and wrote part of the manuscript. PV conceived the study and revised the manuscript for important intellectual content. PM-V has full access to the data and is the guarantor of the manuscript. All authors have read and approved this version of the manuscript.

PATIENT CONSENT FORM

Not applicable

DATA SHARING STATEMENT

Non-identifiable individual-level data are available for researchers who seek to answer questions related to health and disease in the context of research projects who meet the criteria for data sharing by research committees. Please follow the instructions at https://www.colaus-psycolaus.ch/ for information on how to submit an application for gaining access to CoLaus data.

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Not applicable.

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FATIGUE DURANT LA SEMAINE DERNIÈRE

Lisez chaque affirmation et entourez un nombre de 1 à 7 qui semble correspondre à votre état de fatigue durant la semaine dernière.

- Une valeur basse (1) indique que vous n'êtes pas d'accord avec l'affirmation, tandis qu'une valeur haute (7) indique que vous êtes d'accord avec l'affirmation proposée.
- Il est important d'entourer un nombre (1 à 7) pour chaque question.

Durant la semaine passée j'ai trouvé que…	Pas d'accord ⟷ D'accord						
Ma motivation est plus basse quand je suis fatigué (e)	1	2	3	4	5	6	7
Les exercices entrainent une fatigue	1	2	3	4	5	6	7
Je suis facilement fatigué(e)	1	2	3	4	5	6	7
La fatigue interfère avec mon fonctionnement physique	1	2	3	4	5	6	7
La fatigue me cause souvent des problèmes	1	2	3	4	5	6	7
Ma fatigue empêche des activités physiques soutenues	1	2	3	4	5	6	7
La fatigue m'empêche de mener à bien certaines obligations et responsabilités	1	2	3	4	5	6	7
La fatigue est parmi mes 3 symptômes les plus handicapants	1	2	3	4	5	6	7
La fatigue interfère avec mon travail, ma famille ou ma vie sociale	1	2	3	4	5	6	7

Index de sévérité de l'insomnie (ISI)

Instructions

Vos réponses doivent correspondre aux expériences que vous avez eues au cours des derniers mois. Répondez s'il vous plaît à toutes les questions.

Antécédents personnels de difficultés de sommeil :

1. Combien d'heures de sommeil dormez-vous lors d'une nuit habituelle ? _____ heures
2. Considérez-vous que vous avez un problème de sommeil actuellement ? OUI NON
3. Utilisez-vous actuellement des médicaments ou autres substances pour vous aider à dormir ? OUI NON
   Si votre réponse est NON aux deux questions précédentes (n° 2 et 3), passez directement à la question n° 14.
4. Veuillez estimer la **SÉVÉRITÉ** actuelle (dernier mois) de vos difficultés de sommeil.
   a. Difficultés d'endormissement :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

   b. Difficulté de maintien du sommeil :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

   c. Réveil trop précoce le matin :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

5. Êtes-vous actuellement **SATISFAIT(E)/INSATISFAIT(E)** de votre sommeil ?

Très Satisfait	Satisfait	Modérément Satisfait	Insatisfait	Très Insatisfait
0	1	2	3	4

6. À quel point considérez-vous que vos difficultés de sommeil **PERTURBENT** votre fonctionnement quotidien (par exemple, fatigue, concentration, mémoire, humeur) ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

7. À quel point considérez-vous que vos difficultés de sommeil sont **REMARQUÉES** par les autres en termes de détérioration de votre qualité de vie ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

8. À quel point êtes-vous **INQUIET(E)/PRÉOCCUPÉ(E)** par vos difficultés actuelles de sommeil ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

9. Depuis combien de temps ressentez-vous des difficultés de sommeil ?
   En mois : (nombre)
   En années : (nombre)

10. Combien de nuits par semaine pensez-vous avoir des (nombre) difficultés de sommeil ?
    Par semaine (nombre)

11. Avez-vous de la difficulté à rester éveillé le jour ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

12. Avez-vous d'autres difficultés de sommeil ? Si oui, veuillez en préciser la nature :
    _____ cauchemars, _____ difficultés à respirer, _____ ronflement, _____ parler dans votre sommeil, _____ marcher dans votre sommeil, _____ mouvements des membres inférieurs.

13. À quel âge, vos difficultés de sommeil ont-elles débuté ? _____ ans
    Veuillez passer à la question n° 15.

14. **Histoire :**
    Avez-vous eu dans le passé des difficultés de sommeil ayant persisté pour plus d'un mois ?
    OUI NON
    Si non, veuillez passer à la question n° 15.
    Si oui, pour quelle durée ? _____ mois _____ années
    Quel âge aviez-vous à ce moment ? _____ ans
    Quelle était la nature de ces difficultés ? _____
    (voir question n° 12).

15. Souffrez-vous actuellement d'un trouble anxieux ou dépressif ?

16. Prenez-vous actuellement un traitement à visée psychologique ?

Score

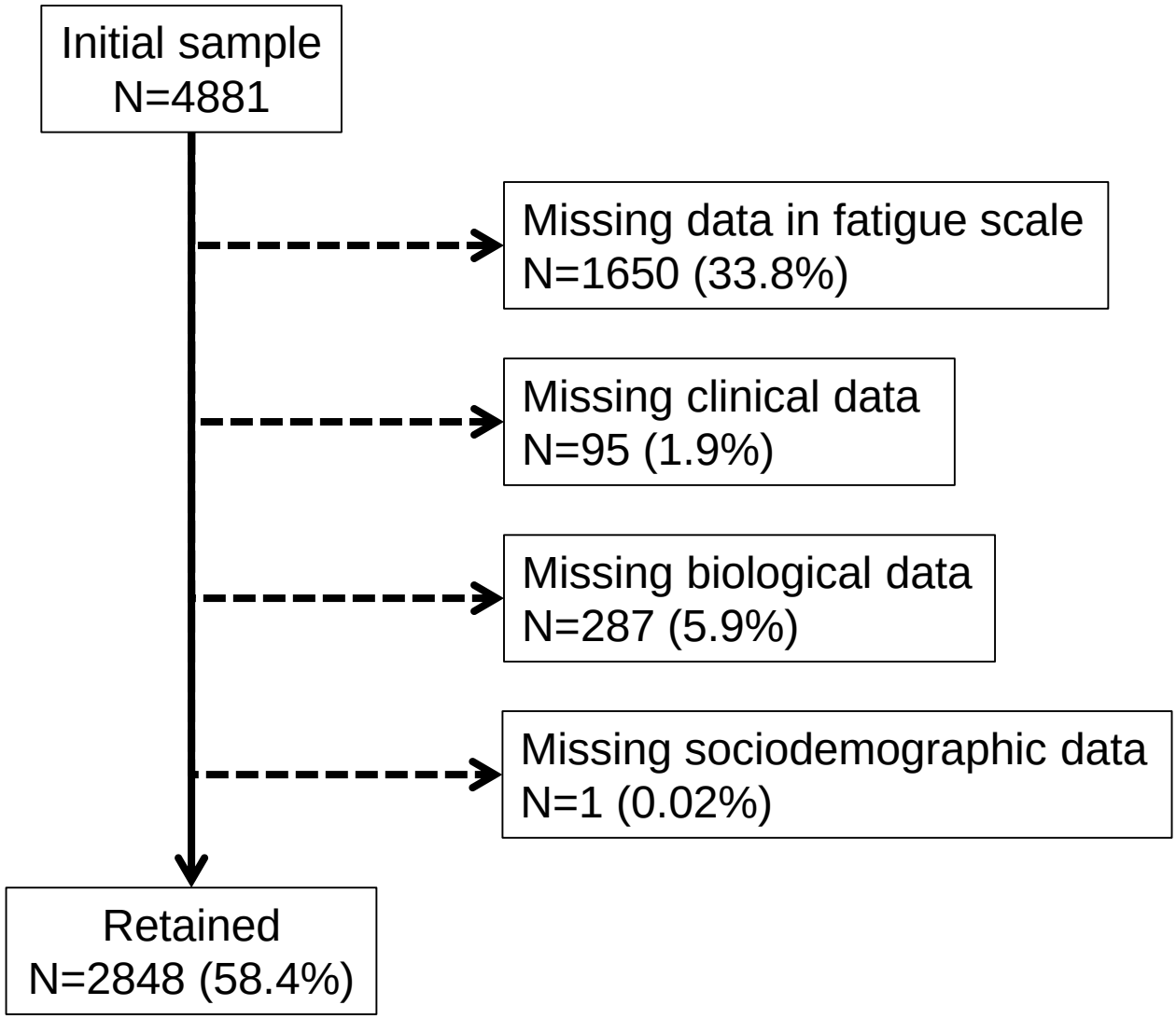
Pour analyser et interpréter ce questionnaire, additionnez les notes données aux questions 4a, 4b, 4c, 5, 6, 7 et 8. Le score total s'établit entre 0 et 28.

0–7	Pas d'insomnie
8–14	Insomnie légère
15–21	Insomnie modérée
22–28	Insomnie sévère

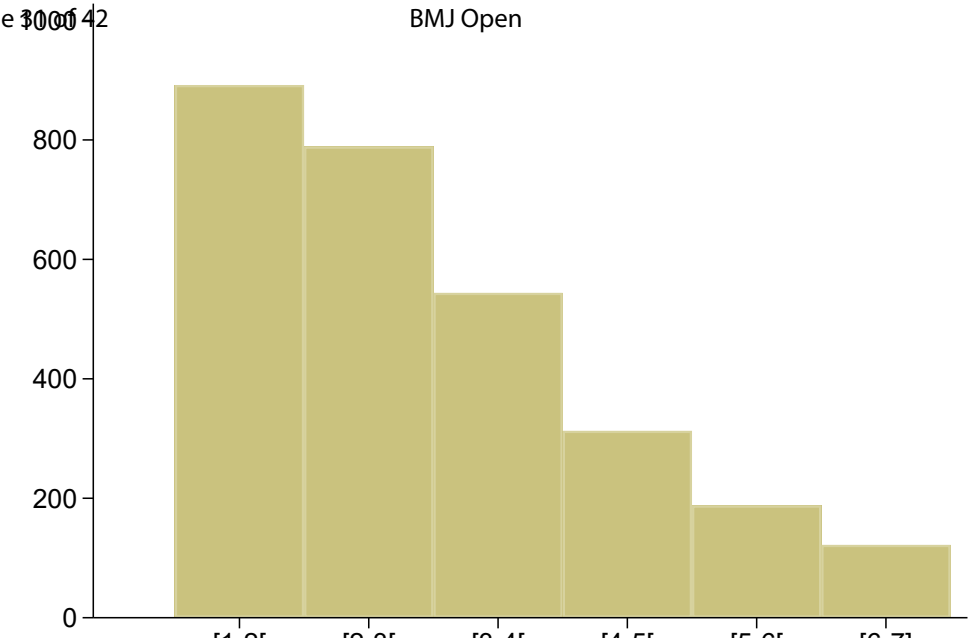
Référence

Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001 ; 2 : 297–307.

Supplemental figure 1: The reasons for exclusion



Exclusion if missing data in fatigue scale, missing clinical, biological and sociodemographic data



Supplemental table 1: comparison between excluded and included participants

	Included	Excluded	p-value
N	2848	2033	
Woman (%)	1514 (53.2)	1175 (57.8)	0.001
Age (years)	61.5 ± 9.8	65.0 ± 11.0	<0.001
Age groups			<0.001
45-54	879 (30.9)	467 (23.0)	
55-64	933 (32.8)	569 (28.0)	
64-74	739 (26.0)	560 (27.6)	
75+	297 (10.4)	437 (21.5)	
Educational level			<0.001
University	683 (24.0)	348 (17.2)	
High school	808 (28.4)	450 (22.2)	
Apprenticeship	1015 (35.6)	734 (36.2)	
Primary	342 (12.0)	497 (24.5)	
Smoking categories			0.015
Never	1149 (41.3)	737 (43.1)	
Former	1130 (40.6)	624 (36.5)	
Current	505 (18.1)	350 (20.5)	
BMI (kg/m^2)	26.4 ± 4.5	26.5 ± 5.0	0.525
BMI categories			0.038
Underweight	42 (1.5)	33 (2.0)	
Normal	1139 (40.0)	643 (39.4)	
Overweight	1157 (40.6)	618 (37.8)	
Obese	510 (17.9)	339 (20.8)	
Caffeinated drinks			<0.001
None	280 (10.1)	182 (11.3)	
1-3/day	1792 (64.7)	1108 (69.0)	
4-6/day	608 (21.9)	272 (16.9)	
7+/day	92 (3.3)	44 (2.7)	
Self-rated health			<0.001
Very good	679 (23.8)	353 (17.8)	
Good	1617 (56.8)	1094 (55.2)	
Average	502 (17.6)	464 (23.4)	
Bad + Very bad	50 (1.8)	72 (3.6)	
Cardiovascular disease	245 (8.6)	274 (13.5)	<0.001
Diabetes	226 (8.0)	256 (15.0)	<0.001
Depression	329 (11.9)	93 (11.9)	0.971
Anemia	109 (3.8)	108 (6.5)	<0.001
Ferritin [mcg/l]	227 [147 - 2.97]	220 [141 - 2.93]	0.058
TSH [mUI/l]	3.0 [2.1 - 3.0]	3.0 [2.1 - 2.9]	0.375
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 3.3	0.534
Anti-hypertensive drugs	885 (31.1)	812 (39.9)	<0.001
Anti-histaminics	68 (2.4)	32 (1.6)	0.048
Antidepressants	278 (9.8)	246 (12.1)	0.009
Hypnotics	122 (4.3)	145 (7.1)	<0.001

BMI, body mass index. Results are expressed as number of participants (column percentage) for categorical variables and as average±standard deviation or median [interquartile range] for continuous variables. Between-group comparison performed using chi-square for categorical variables and using student's t-test or Kruskal-Wallis test (§) for continuous variables.

Supplemental table 2: variables used to compute the propensity score

	Odds ratio (95% CI)	p-value
Gender (woman vs. man)	0.77 (0.64 - 0.93)	0.006
Age groups		
45-54	1 (ref)	
55-64	0.85 (0.68 - 1.07)	0.178
64-74	0.81 (0.63 - 1.03)	0.083
75+	0.50 (0.37 - 0.67)	<0.001
Educational level		
Primary	1 (ref)	
Apprenticeship	1.45 (1.11 - 1.91)	0.007
High school	1.58 (1.19 - 2.10)	0.002
University	1.51 (1.12 - 2.04)	0.007
Smoking categories		
Never	1 (ref)	
Former	1.15 (0.95 - 1.39)	0.155
Current	1.08 (0.85 - 1.39)	0.523
BMI categories		
Underweight	0.80 (0.43 - 1.49)	0.479
Normal	1 (ref)	
Overweight	1.39 (1.14 - 1.69)	0.001
Obese	1.57 (1.20 - 2.05)	0.001
Caffeinated drinks		
None		
1-3/day	1.14 (0.86 - 1.51)	0.369
4-6/day	1.29 (0.93 - 1.78)	0.129
7+/day	1.16 (0.66 - 2.03)	0.599
Self-rated health		
Very good	1 (ref)	
Good	0.98 (0.79 - 1.21)	0.836
Average	1.08 (0.80 - 1.45)	0.610
Bad + Very bad	1.22 (0.55 - 2.73)	0.621
Diabetes (yes vs. no)	0.69 (0.50 - 0.94)	0.021
Anemia (yes vs. no)	0.82 (0.54 - 1.26)	0.369

BMI, body mass index. Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Multivariable analysis performed using logistic regression.

Supplemental table 3: Bivariate and multivariable analysis of the continuous determinants of fatigue as defined by a Fatigue Severity Scale ≥5 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2538	310		2538	310	
Age (years)	61.7 ± 9.8	60.0 ± 10.0	0.005			
BMI (kg/m^2)	26.2 ± 4.4	27.8 ± 5.4	<0.001			
Handgrip (kg)	35.0 ± 12.0	32.8 ± 11.4	0.002	35.1 ± 0.1	35.4 ± 0.5	0.453
Ferritin [mcg/l]	149 [91 - 229]	138 [84 - 208]	0.083 §	185.1 ± 3.5	205.1 ± 11.3	0.098
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 3.0]	1.000 §	2.5 ± 0.1	2.5 ± 0.1	0.987
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 2.6	0.968	16.3 ± 0.1	16.2 ± 0.2	0.881

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, self-rated health and depression.

Supplemental table 4: Bivariate and multivariable analysis of the categorical determinants of fatigue as defined by a Fatigue Severity Scale ≥5 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable model 1		Multivariable model 2	
	No fatigue	**Fatigue**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Gender			0.011				
Man	1210 (47.7)	124 (40.0)		1 (ref)		1 (ref)	
Woman	1328 (52.3)	186 (60.0)		1.45 (1.05 - 1.99)	0.024	1.43 (1.04 - 1.95)	0.027
Age group			<0.001				
45-54	758 (29.9)	121 (39)		1 (ref)		1 (ref)	
55-64	829 (32.7)	104 (33.6)		0.70 (0.49 – 1.00)	0.051	0.70 (0.49 - 0.99)	0.045
64-74	691 (27.2)	48 (15.5)		0.42 (0.27 - 0.64)	<0.001	0.41 (0.26 - 0.63)	<0.001
75+	260 (10.2)	37 (11.9)		0.81 (0.48 - 1.35)	0.416	0.79 (0.48 - 1.32)	0.370
Educational level			0.106				
Primary	293 (11.5)	49 (15.8)		1 (ref)			
Apprenticeship	905 (35.7)	110 (35.5)		1.03 (0.64 - 1.67)	0.902	-	
High school	720 (28.4)	88 (28.4)		1.11 (0.67 - 1.82)	0.687	-	
University	620 (24.4)	63 (20.3)		1.10 (0.65 - 1.86)	0.728	-	
Smoking categories			0.762				
Never	1028 (41.4)	121 (40.2)		-		-	
Former	1002 (40.4)	128 (42.5)		-		-	
Current	453 (18.2)	52 (17.3)		-		-	
BMI categories			<0.001				
Underweight	41 (1.6)	1 (0.3)		0.22 (0.03 - 1.85)	0.162	0.22 (0.03 - 1.85)	0.162
Normal	1032 (40.7)	107 (34.5)		1 (ref)		1 (ref)	
Overweight	1041 (41.0)	116 (37.4)		0.94 (0.66 - 1.34)	0.742	0.94 (0.66 - 1.33)	0.715
Obese	424 (16.7)	86 (27.7)		1.40 (0.93 - 2.08)	0.103	1.38 (0.93 - 2.06)	0.109
Insomnia categories			<0.001				
No insomnia	1972 (84.3)	145 (54.9)		1 (ref)		1 (ref)	
Subthreshold	288 (12.3)	59 (22.4)		1.45 (0.98 - 2.16)	0.064	1.46 (0.98 - 2.15)	0.060
Clinical insomnia	79 (3.4)	60 (22.7)		3.90 (2.41 - 6.33)	<0.001	3.82 (2.36 - 6.18)	<0.001
Caffeinated drinks			0.278				
None	240 (9.7)	40 (13.3)		-		-	

1-3/day	1603 (64.9)	189 (62.8)		-		-	
4-6/day	546 (22.1)	62 (20.6)		-		-	
7+/day	82 (3.3)	10 (3.3)		-		-	
Self-rated health			<0.001				
Very good	656 (25.9)	23 (7.4)		1 (ref)		1 (ref)	
Good	1505 (59.3)	112 (36.1)		1.61 (0.98 - 2.64)	0.062	1.58 (0.96 - 2.60)	0.069
Average	358 (14.1)	144 (46.5)		5.80 (3.40 - 9.87)	<0.001	5.65 (3.34 - 9.58)	<0.001
Bad + Very bad	19 (0.8)	31 (10.0)		17.7 (7.32 - 42.6)	<0.001	17.2 (7.16 - 41.1)	<0.001
Cardiovascular disease			0.617				
No	2322 (91.5)	281 (90.7)		-		-	
Yes	216 (8.5)	29 (9.4)		-		-	
Diabetes			0.006				
No	2343 (92.5)	273 (88.1)		1 (ref)		1 (ref)	
Yes	189 (7.5)	37 (11.9)		0.99 (0.58 - 1.70)	0.975	0.99 (0.58 - 1.69)	0.979
Depression (CES-D)			<0.001				
No	2260 (91.8)	170 (57.4)		1 (ref)		1 (ref)	
Yes	203 (8.2)	126 (42.6)		3.31 (2.28 - 4.79)	<0.001	3.34 (2.31 - 4.83)	<0.001
Anemia			0.325				
No	2444 (96.3)	295 (95.2)		1 (ref)		-	
Yes	94 (3.7)	15 (4.8)		1.24 (0.60 - 2.59)	0.557	-	
Ferritin categories			0.971				
>50	2294 (90.4)	280 (90.3)		-		-	
Normal + low	244 (9.6)	30 (9.7)		-		-	
TSH categories			0.842				
High > 4.22	223 (8.8)	30 (9.7)		1.50 (0.92 - 2.44)	0.105	-	
Normal 0.27-4.22	2294 (90.4)	277 (89.4)		1 (ref)		-	
Low < 0.27	21 (0.8)	3 (1.0)		0.63 (0.13 - 3.11)	0.566	-	
Free T4 categories			0.636				
High > 22	58 (2.3)	6 (1.9)		-		-	
Normal 12-22	2419 (95.3)	294 (94.8)		-		-	
Low < 12	61 (2.4)	10 (3.2)		-		-	
Anti-hypertensive			0.461				
No	1755 (69.2)	208 (67.1)		-		-	

Yes	783 (30.9)	102 (32.9)		-		-	
Anti-histaminics			0.156				
No	2481 (97.8)	299 (96.5)		1 (ref)		-	
Yes	57 (2.3)	11 (3.6)		1.06 (0.47 - 2.42)	0.882	-	
Antidepressants			<0.001				
No	2330 (91.8)	240 (77.4)		1 (ref)		1 (ref)	
Yes	208 (8.2)	70 (22.6)		1.48 (0.97 - 2.25)	0.070	1.46 (0.96 - 2.21)	0.076
Hypnotics			0.004				
No	2439 (96.1)	287 (92.6)		1 (ref)		1 (ref)	
Yes	99 (3.9)	23 (7.4)		0.61 (0.31 - 1.23)	0.167	0.63 (0.31 - 1.26)	0.190

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Two multivariable models were applied: model 1 included all variables significantly ($p<0.05$) associated with fatigue using the threshold of ≥4 of the fatigue severity scale, while model 2 included only the variables significantly ($p<0.05$) associated with fatigue using the threshold of ≥5 of the fatigue severity scale.

Supplemental table 5: Multivariable analysis of the categorical determinants of fatigue (defined as a fatigue severity score ≥4) in the CoLaus study, Lausanne, Switzerland, 2014-2017, using inverse probability weighting.

	OR (95% CI)	P-value
Gender (woman vs. man)	1.26 (0.99 - 1.61)	0.064
Age group		
45-54	1 (ref)	
55-64	0.70 (0.53 - 0.91)	0.009
64-74	0.43 (0.31 - 0.59)	<0.001
75+	0.64 (0.42 - 0.96)	0.031
Educational level		
Primary	1 (ref)	
Apprenticeship	1.02 (0.70 - 1.48)	0.923
High school	1.08 (0.74 - 1.59)	0.678
University	0.94 (0.63 - 1.41)	0.768
BMI categories		
Underweight	0.71 (0.20 - 2.56)	0.598
Normal	1 (ref)	
Overweight	1.03 (0.79 - 1.34)	0.833
Obese	1.44 (1.05 - 1.98)	0.022
Insomnia categories		
No insomnia	1 (ref)	
Subthreshold	1.57 (1.15 - 2.14)	0.004
Clinical insomnia	3.74 (2.29 - 6.10)	<0.001
Self-rated health		
Very good	1 (ref)	
Good	1.92 (1.37 - 2.69)	<0.001
Average	5.51 (3.71 - 8.17)	<0.001
Bad + Very bad	17.2 (7.51 - 39.3)	<0.001
Diabetes (yes vs. no)	1.15 (0.76 - 1.74)	0.501
Depression (CES-D, yes vs. no)	3.21 (2.34 - 4.42)	<0.001
Anemia (yes vs. no)	1.58 (0.91 - 2.76)	0.107
TSH categories		
High > 4.22	1.15 (0.77 - 1.70)	0.499
Normal 0.27-4.22	1 (ref)	
Low < 0.27	3.30 (1.09 - 10.0)	0.035
Anti-histaminics (yes vs. no)	1.33 (0.69 - 2.57)	0.398
Antidepressants (yes vs. no)	1.39 (0.98 - 1.97)	0.069
Hypnotics (yes vs. no)	0.59 (0.31 - 1.10)	0.098

Results are expressed as multivariable-adjusted odds ratio (OR) and (95% confidence interval - CI). Multivariable analysis performed using logistic regression with inverse probability weighting.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Suppl figure 1
		(b) Give reasons for non-participation at each stage	Suppl figure 1
		(c) Consider use of a flow diagram	Suppl figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl table 1

		(b) Indicate number of participants with missing data for each variable of interest	Suppl figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl table 2-3-4-5
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

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Prevalence and factors associated with fatigue in the Lausanne middle-aged population: A population based cross-sectional survey

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Prevalence and factors associated with fatigue in the Lausanne middle-aged population: A population based cross-sectional survey

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Abstract

Objective: To assess the prevalence and factors associated with fatigue in the general population.

Design: Population based cross-sectional survey performed between May 2014 and April 2017.

Setting: General population of the city of Lausanne, Switzerland.

Participants: 2848 participants (53.2% women, age range 45-86 years).

Primary outcome measure: Prevalence of fatigue the previous week, defined as a score ≥4 using the Fatigue Severity Scale (FSS).

Results: The prevalence of fatigue was 21.9% (95% CI: 20.4% – 23.4%) in the total sample. On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels. Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression, low TSH values, had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad. Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated with fatigue; while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics.

Conclusion: In a population-based sample aged 45 to 86, fatigue was present in one out of five subjects. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea should be assessed first, followed by depression. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step. Sleep complaints and fatigue in older subjects are not due to aging and should prompt the identification of the underlying cause.

Keywords: fatigue; prevalence; epidemiology; Fatigue severity scale

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study assessed the prevalence and factors associated with fatigue in a general population setting.
- A large panel of associated with fatigue was evaluated.
- A list of the most frequent determinants was established, facilitating etiological search in clinical practice
- The study was limited to subjects aged 45 to 86, so results do not apply to younger or older groups.

INTRODUCTION

Fatigue is usually defined as "an unpleasant physical, cognitive and emotional symptom described as a tiredness not relieved by common strategies that restore energy".[1] Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities.[1] Indeed, fatigue is a common symptom with prevalence rates varying between 4 and 45%.[2-4] This ten-fold range in prevalence rates is likely due to the different settings (i.e. general practice [5] or workers [6]) or the different methods used to assess fatigue. [7]

In healthy subjects, tiredness or sleepiness are a natural occurrence after physical or mental efforts, and are usually relieved by rest. [8 9] While fatigue is defined as extreme and persistent tiredness, weakness or exhaustion, of mental and/or physical origin [7] that is not relieved by rest. Fatigue is defined in duration as recent (<1 month) prolonged (1 to 6 months) and chronic (>6 months) [10]. When unexplained, chronic fatigue can be considered either as a syndrome (characterized by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches) [11] or as idiopathic (absence of other symptoms).

Fatigue is one of the most common complaints reported in primary care [12] and is associated with a decreased quality of life and increased morbidity and mortality in the general population. [13] Fatigue is a multidimensional concept, and several determinants have been proposed. Although a cause (somatic or psychiatric) is identifiable in 2/3 of fatigue cases, 1/3 of fatigue cases still have no specific diagnosis.[10] The most frequent diagnoses associated with fatigue are viral or upper respiratory tract infection, iron deficiency anemia, adverse effects of medication, depression or other mental disorders.[14] Fatigue has also been associated with female sex, [8 15] older age [16 17] and lower socioeconomic status, [16 17] although the association with the last two determinants were not found in some studies. [8 18] Importantly, most studies on fatigue have been conducted in selected populations such as workers [6] or general practice attendees.[2 5 18] To our knowledge, only two studies have assessed the prevalence of fatigue in the general population [8 19] and only a few have explored the

determinants of fatigue in the general population.[13 15-17 20 21] Furthermore, most studies focused on socio-economic and disease determinants of fatigue, while information regarding the biological determinants (i.e. anemia or thyroid pathology) [13] or the medications associated with fatigue is scarce. Moreover, to date, little is known about the prevalence of fatigue and its determinants in Switzerland.

Hence, this study aimed to examine the prevalence and the factors associated with fatigue in a population-based sample from the city of Lausanne, Switzerland.

POPULATION AND METHODS

Study population

The CoLaus study is a population-based cohort exploring biological, genetic, and environmental determinants of cardiovascular diseases. Detailed descriptions of the study design have been reported elsewhere.[22] Briefly, a non-stratified random representative sample of the population of Lausanne was recruited between 2003 and 2006 using the following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate. The first follow-up was performed between April 2009 and September 2012 and the second follow-up between May 2014 and April 2017, 10.9 years on average after the baseline study. At both baseline and subsequent follow-ups, participants were invited to attend a clinical examination at the Lausanne university hospital. Participants received a paper questionnaire at home, which they filled prior to the clinical examination. During the clinical examination, a second questionnaire regarding personal and family history of cardiovascular disease and cardiovascular risk factors was applied. For more details, please consult www.colaus-psycolaus.ch.

As fatigue was only assessed in the second follow-up, data from the second follow-up, which included 4881 of the initial 6773 participants recruited at baseline, was used. At the second follow-up, participants were aged 45-86 years.

Fatigue scale

Fatigue severity during the previous week was assessed by the 9 items Fatigue Severity Scale (FSS). [9] The FSS is one of the most commonly used fatigue questionnaires. It had been validated in a healthy population setting in German-speaking Switzerland [23], Portugal [24] and Norway [19]. It is a simple, time-saving, self-administrated questionnaire allowing its use in large epidemiological studies and has a high test-retest reliability. [7] The questionnaire is composed of nine questions; responses are graded using a Likert scale from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement. The final score is the mean value of the nine responses, and a score ≥4 is considered as having severe fatigue. This cutoff was initially proposed because <5% of healthy controls rate their fatigue at that level, whereas 60-90% of patients with medical disorders experience fatigue at or above this level. [9] An example of the questionnaire in French is provided in **Annex 1,** in English in **Annex 2**. To our knowledge, the French version of the FSS has not yet been validated in Switzerland. Still, the Cronbach's alpha for the questionnaire was 0.918, suggesting an excellent internal consistency.

Covariates

Socioeconomic and lifestyle variables were collected using a self-administered questionnaire. Smoking status was categorized into never, former and current smoker. Educational level was collected at baseline and categorized as obligatory school, apprenticeship, high school/college or university.

Insomnia was assessed using the Insomnia Severity Index (ISI).[25] The questionnaire has 16 items evaluating the nature, severity, and impact of insomnia over the last month; namely difficulties falling asleep, sleep maintenance problems, and early morning awakening, sleep dissatisfaction, interference of sleep disturbances with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Responses range from 0 "Not at all" to 4 "Extremely". Items were scaled 0-4 and then summed to obtain the

global ISI score (range: 0-28). The questionnaire is provided in **Annex 3**. Clinically significant insomnia was defined as an ISI score ≥15 (moderate to severe intensity).[25]

Depression was assessed with the CES-D [26], a 20 item self-report instrument, developed for research in the general population, that is used to assess the severity of depressive symptoms over the past week on a 4-point scale. It was translated into French by Fuhrer and Rouillon.[27] It has been used in other recent epidemiological studies assessing the link between depression and cardiovascular risk factors [28]. The questionnaire is composed of 20 questions; responses are graded from 0 to 3, where 0 indicates rarely or never (less than one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the 20 responses (possible range is 0-60), and a score ≥16 is considered as a risk for depression.

Self-rated health was assessed by a single question where participants had to rate their current health status from five categories ranging from “very bad” to “very good”. As the number of participants rating their health as “very bad” was very small, they were grouped with the participants who rated their health as “bad”.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight/height^2 and categorized as underweight (BMI<18.5 kg/m^2), normal (18.5≤BMI<25 kg/m^2); overweight (25≤ BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2).

Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and 30° of dorsiflexion. Three measurements were performed consecutively with the right hand and the highest value (expressed in kg) was included in the analyses.

Caffeinated drink consumption was assessed by the question “How many cups or cans of drinks containing caffeine (coffee, tea, coke or similar) do you drink per day?” with possible answers “None”, “1-3”, “4-6” and “7 or more”.

Participants were asked to report all medications (prescribed or bought over the counter) they took during the last 6 months. Medications were coded using the Anatomical, Therapeutic Chemical (ATC) classification of the world health organization (www.whocc.no/atc_ddd_index/). Antihistamics were defined as any ATC code beginning with “R06”; antidepressants were defined as an ATC code beginning with “N05BD" or N06AA" or “N06AB" or “N06AF" or “N06AG" or “N06AX" or “N06CA"; hypnotics were defined as any ATC code beginning with “N05C”. Antihypertensive drugs were defined by asking the participants if they were taking drugs for hypertension.

Diabetes was defined by a fasting plasma glucose ≥7 mmol/L and/or the presence of an antidiabetic drug treatment (oral or insulin). Personal history of cardio vascular disease was assessed by asking the participant if he/she had sustained a coronary event (myocardial infarction or angina pectoris) or a stroke.

Biological assays were performed by the CHUV Clinical Laboratory on fresh blood samples within 2 hours of blood collection, and additional aliquots were stored at –80°C. All measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland). The following analytical procedures (with maximum inter and intra-batch CVs) were used: high sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by immunoturbidimetric method (Tina-quant 4th generation, Roche Diagnostics, Switzerland) with a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid stimulating hormone (TSH) and free T_4 were assessed by chemiluminescence (ECLIA) on a Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free T_4.

Exclusion criteria

Participants were excluded if they lacked 1) any answer to the fatigue questionnaire; 2) clinical data such as age, body mass index, smoking, depression, insomnia or medications; 3) biological measures such as haemoglobin or thyroid hormones and 4) socioeconomic data such as educational level.

Ethical statement and consent

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-up. The full decisions of the CER-VD can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Patient and Public Involvement

No patients or public were involved in this study design, conduct or analysis.

Statistical analysis

Statistical analysis was performed using Stata version 15.1 for windows (Stata Corp, College Station, Texas, USA). Prevalence rates for fatigue were expressed as percentage and 95% confidence interval (CI). Descriptive results were expressed as number of participants (percentage) for categorical variables or as average±standard deviation for continuous variables. Bivariate analyses were performed using chi-square or Fisher's exact test for categorical variables and student's t-test or Kruskal-Wallis test for continuous variables. All categorical variables significantly ($p<0.05$) associated with fatigue in the bivariate analysis were included in the multivariable analysis. Multivariable analysis was performed using analysis of variance or logistic regression with fatigue (dichotomized into yes/no) as dependent variable; results were expressed as multivariable-adjusted mean±standard error for continuous variables or as Odds ratio (OR) and 95% CI for categorical variables.

Sensitivity analyses were conducted using a FSS threshold of 5. Further, as the number of excluded participants was high, other sensitivity analyses were conducted by creating a propensity score for being excluded [29]. The propensity score was computed using logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly associated with exclusion as independent variables. A probability of exclusion was computed for each participant, and the inverse of the probability was used for weighting.

Statistical significance was assessed for a two-sided test with $p<0.05$.

Results

Study population

Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most frequent reason was lack of data regarding fatigue. The comparison between included and excluded participants is provided in **supplemental table 1** and the results of the multivariable analysis are provided in **supplemental table 2**. Excluded participants were more frequently women, were older, had a lower educational level, were more frequently never or current smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and hypertension) and rated their health worse.

Prevalence and factors associated with fatigue

The overall prevalence of fatigue as defined by a FSS ≥4 was 21.9% (95% CI: 20.4% – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% - 22.3%), p=0.031. The distribution of the FSS ≥5 (prevalence of fatigue 10.9%) is provided in **supplemental figure 2**; the number of participants with fatigue decreased when the levels of FSS increased.

The analysis of the factors associated with fatigue as defined by a FSS ≥4 is provided in **Tables 1 and 2**.

Table 1: Bivariate and multivariable analysis of the continuous factors associated with fatigue as defined by a Fatigue Severity Scale ≥4 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2225	623				
Age (years)	61.9 ± 9.8	60.0 ± 9.8	<0.001	-	-	
BMI (kg/m^2)	26.1 ± 4.4	27.4 ± 5.0	<0.001	-	-	
Handgrip (kg)	35.0 ± 12.0	33.8 ± 12.0	0.022	35.0 ± 0.2	35.3 ± 0.3	0.430
Ferritin [mcg/l]	149 [92-229]	139 [83-214]	0.034 §	188 ± 4	185 ± 8	0.732
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 2.9]	0.374 §	2.5 ± 0.1	2.4 ± 0.1	0.332
Free T4 [pmol/l]	16.2 ± 2.5	16.3 ± 2.6	0.190	16.2 ± 0.1	16.4 ± 0.1	0.221

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, self-rated health and depression.

Table 2: Bivariate and multivariable analysis of the categorical factors associated with fatigue as defined by a Fatigue Severity Scale ≥4 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable	
	No fatigue	**Fatigue**	**p-value**	**OR (95% CI)**	**p-value**
Gender			0.031		
Man	1066 (47.9)	268 (43.0)		1 (ref)	
Woman	1159 (52.1)	355 (57.0)		1.25 (0.99 - 1.58)	0.065
Age group			<0.001		
45-54	643 (28.9)	236 (37.9)		1 (ref)	
55-64	724 (32.5)	209 (33.6)		0.69 (0.53 - 0.90)	0.006
64-74	626 (28.1)	113 (18.1)		0.43 (0.31 - 0.59)	<0.001
75+	232 (10.4)	65 (10.4)		0.60 (0.40 - 0.90)	0.013
Educational level			0.017		
Primary	249 (11.2)	93 (14.9)		1 (ref)	
Apprenticeship	794 (35.7)	221 (35.5)		1.05 (0.73 - 1.51)	0.782
High school	626 (28.1)	182 (29.2)		1.13 (0.78 - 1.64)	0.520
University	556 (25.0)	127 (20.4)		0.98 (0.66 - 1.46)	0.937
Smoking categories			0.279		
Never	907 (41.7)	242 (39.7)		-	
Former	866 (39.8)	264 (43.4)		-	
Current	402 (18.5)	103 (16.9)		-	
BMI categories			<0.001		
Underweight	37 (1.7)	5 (0.8)		0.69 (0.24 - 2.01)	0.495
Normal	920 (41.4)	219 (35.2)		1 (ref)	
Overweight	914 (41.1)	243 (39.0)		1.01 (0.78 - 1.31)	0.942
Obese	354 (15.9)	156 (25.0)		1.40 (1.03 - 1.91)	0.032
Insomnia categories			<0.001		
No insomnia	1782 (86.2)	335 (62.6)		1 (ref)	
Subthreshold	233 (11.3)	114 (21.3)		1.57 (1.16 - 2.13)	0.003
Clinical insomnia	53 (2.6)	86 (16.1)		3.76 (2.41 - 5.86)	<0.001
Caffeinated drinks			0.147		
None	205 (9.5)	75 (12.3)		-	
1-3/day	1418 (65.5)	374 (61.5)		-	
4-6/day	471 (21.8)	137 (22.5)		-	
7+/day	70 (3.2)	22 (3.6)		-	
Self-rated health			<0.001		
Very good	621 (27.9)	58 (9.3)		1 (ref)	
Good	1323 (59.5)	294 (47.2)		1.94 (1.39 - 2.71)	<0.001
Average	270 (12.1)	232 (37.2)		5.55 (3.78 - 8.14)	<0.001
Bad + Very bad	11 (0.5)	39 (6.3)		14.1 (5.95 - 33.4)	<0.001
Cardiovascular disease			0.697		
No	2036 (91.5)	567 (91.0)		-	
Yes	189 (8.5)	56 (9.0)		-	
Diabetes			<0.001		
No	2069 (93.2)	547 (87.9)		1 (ref)	
Yes	151 (6.8)	75 (12.1)		1.24 (0.82 - 1.87)	0.306
Depression (CES-D)			<0.001		
No	2026 (93.8)	404 (67.6)		1 (ref)	
Yes	135 (6.3)	194 (32.4)		3.26 (2.38 - 4.46)	<0.001
Anemia			0.008		
No	2151 (96.7)	588 (94.4)		1 (ref)	

Yes	74 (3.3)	35 (5.6)		1.70 (1.00 - 2.89)	0.049
Ferritin categories			0.436		
>50	2016 (90.6)	558 (89.6)		-	
Normal + low	209 (9.4)	65 (10.4)		-	
TSH categories			0.017		
High > 4.22	197 (8.9)	56 (9.0)		1.13 (0.77 - 1.66)	0.533
Normal 0.27-4.22	2015 (90.6)	556 (89.3)		1 (ref)	
Low < 0.27	13 (0.6)	11 (1.8)		2.50 (0.91 - 6.85)	0.075
Free T4 categories			0.651		
High > 22	47 (2.1)	17 (2.7)		-	
Normal 12-22	2122 (95.4)	591 (94.9)		-	
Low < 12	56 (2.5)	15 (2.4)		-	
Anti-hypertensive			0.108		
No	1550 (69.7)	413 (66.3)		-	
Yes	675 (30.3)	210 (33.7)		-	
Anti-histaminics			0.007		
No	2181 (98)	599 (96.2)		1 (ref)	
Yes	44 (2.0)	24 (3.9)		1.30 (0.69 - 2.46)	0.417
Antidepressants			<0.001		
No	2062 (92.7)	508 (81.5)		1 (ref)	
Yes	163 (7.3)	115 (18.5)		1.44 (1.02 - 2.04)	0.040
Hypnotics			<0.001		
No	2146 (96.5)	580 (93.1)		1 (ref)	
Yes	79 (3.6)	43 (6.9)		0.57 (0.32 - 1.03)	0.062

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Only variables with p<0.05 in the bivariate analysis were retained for the multivariable analysis.

On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels (**Table 1**). Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression and low TSH values (**Table 2**). Finally, participants with fatigue had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad (**Table 2**).

Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26

(2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics (**Table 2**).

Sensitivity analyses

The overall prevalence of fatigue as defined by a FSS ≥5 was 10.9% (95% CI: 9.7% – 12.1%) and was higher in women 12.3% (10.7% - 14.0%) than in men 9.3% (7.8% - 11.1%), p=0.011. The results of the sensitivity analyses using a FSS threshold of ≥5 are provided in **supplemental tables 3 and 4**. Overall, the results were comparable with those using a threshold of ≥4: gender, insomnia categories (p-value for trend <0.001), and low self-rated health status (p-value for trend <0.001) were positively associated with fatigue. Conversely, no association was found for age, obesity, diabetes, TSH levels, antihistaminics, antidepressives or hypnotics (**supplemental table 4**).

Sensitivity analysis using inverse probability weighting by the propensity score led to similar findings, except that anemia and antidepressants were no longer associated with fatigue, while a positive association was found between low TSH levels and fatigue (**Supplemental table 5**).

Discussion

To our knowledge, this is one of the few studies assessing the prevalence and the factors associated with fatigue in a general population setting, and the first study conducted in Switzerland. Using a FSS cut-off ≥4, our results indicate that one out of five people aged between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and decreasing self-rated health status were positively associated with fatigue; while older age was negatively associated with fatigue.

Prevalence of fatigue

Using the cut-off of ≥4, fatigue was present in one out of five participants (22.1%), a finding in agreement with the study by Loge et al. [8], which reported a prevalence of 22% among 2323 participants using the Chalder fatigue scale. Conversely, the cross-sectional study by Lerdal et al. [19], which used the FSS in a sample of 1893 participants, reported a prevalence of fatigue of 46.7% and 23.1% using a cut-off of ≥4 and ≥5 respectively, in comparison 22.1% and 10.9% in our study). A study conducted in general practice reported a prevalence of fatigue of 38% using the Chalder fatigue scale,[2] whereas a study conducted in the Dutch working population reported a prevalence of fatigue of 22% using other fatigue measures. [6] Comparison between studies is hampered by the small number of studies assessing the prevalence of fatigue in non-selected samples, the different fatigue scales used and the somewhat different settings (i.e. general population vs. general practice). Still, they provide a first basis for comparison, and it would be important that future studies use similar assessment methods to facilitate comparisons. Overall, our results suggest that the prevalence of fatigue in the Lausanne population is comparable or lower than reported previously.

Clinical and societal factors associated with fatigue

Women tended to report fatigue more frequently than men, but this association was no longer significant after multivariable adjustment. Higher prevalence of fatigue in women has been found in some studies [8 15] but not in others.[18] In a Swedish study conducted in 2014, Engberg et al. [16] considered that this difference could be due to factors related to gender inequalities regarding household responsibilities and child raising, as the gender gap in general fatigue was largest among those aged <55 years.

Younger people reported fatigue more frequently than elderly, a finding in agreement with a Swedish study conducted in 2014. [16] Similarly, a previous study found that older subjects complain less of sleepiness. [30] Still, this association was no longer statistically significant when the cut off of ≥5 was applied to define fatigue, suggesting that young subjects

tend to present with borderline fatigue as suggested previously [19]. Conversely, earlier studies (1990-2000) found a positive association between age and fatigue.[8] [17] [21] A possible explanation for this difference is that older people might have a better quality of life nowadays and are less depressed. Although there is little information regarding trends in quality of life among Swiss elderly, the VLV study [31] concluded that quality of life among Swiss elderly increased in the last 30 years [32]. Indeed, in our study, the lowest prevalence of fatigue was reported by participants aged 64-74 years, which are the "young" retired with few comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and 12.5% in the 45-54 and 55-64 years, respectively, p-value<0.001).

Obese subjects had a higher prevalence of fatigue defined by a FSS ≥4. This finding is in agreement with studies conducted in the USA [33] and in the UK.[13] . Still, this association was no longer statistically significant when the cut off of ≥5 was applied to define fatigue, suggesting that obese subjects tend to present with borderline fatigue as suggested previously [19]. Obesity is a risk factor for sleep apnoea, which leads to increased daytime sleepiness. Still, the association persisted after adjusting for insomnia, a finding in agreement with a previous study that showed that obese subjects have excessive fatigue independently of sleep-disordered breathing.[34] Because it excluded too much subjects, we did not correlate obesity and sleep-disordered breathing in our study. A possible explanation could be the increase in proinflammatory cytokines in obese subjects,[35] which would lead to higher fatigue,[36] but other factors such as decreased physical fitness should be further explored.

A positive association was found between self-reported clinical insomnia and fatigue, and this association was independent of obesity, depression and antidepressant medication. Fatigue is a core symptom of insomnia [34] and a Norwegian study conducted in 2014 showed that reducing insomnia severity led to a concomitant reduction in fatigue.[37] Interestingly, many subjects with sleep complaints do not consult for this issue,[38] which might lead to an

underestimation of its prevalence. Overall, our results suggest that insomnia is an important and underestimated factor of fatigue.

Both depression and antidepressant medication were independently and positively associated with fatigue. The association between depression and fatigue has been repeatedly reported,[13 39-41] and the same applies for antidepressant medication.[3] Our results confirm the known association between depression and fatigue, and suggest that antidepressant treatment might not systematically relieve fatigue among depressive subjects. Furthermore, fatigue is a common side effect of antidepressant therapy and a symptom of depression, making the identification of the cause of fatigue difficult with a possibility of reverse causality (fatigue leading to depression and vice versa). We used a one-dimensional tool to evaluate fatigue (FSS); hence, we cannot distinguish between physical and mental fatigue. There is considerable overlap in phenomenology of fatigue and depression or anxiety but there are some important differences. People with fatigue without psychiatric symptoms tend to attribute their symptoms to external causes. Conversely, most depressed people experience self-blame or lowered self-esteem [42]. Further, fatigue and depression commonly appear together. A study conducted in 2009 by Harvey et al. [43], showed that 7% of fatigued persons have no psychiatric symptoms, but remained at increased risk of later psychiatric disorder independently of the severity of fatigue.

A strong association was found between poor self-rated health and fatigue, a finding also reported elsewhere.[6 16] Low self-rated health has been associated with increased levels of inflammatory markers such as interleukin 6 and CRP,[44] which in turn could trigger fatigue. Conversely, increased fatigue might lead to a lower rating of health status.

Biological factors associated with fatigue

Participants with anemia had a higher likelihood of reporting fatigue. This finding is in agreement with the literature,[45 46] although no association between fatigue and low haemoglobin levels was found in a UK study. [13] A possible explanation is that in the UK study,

anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds used in our study (<133 g/l for men and <117 g/l for women). This led to a small sample size (356 participants, corresponding to 1.9% of the overall sample) and thus a low statistical power.

Hypothyroidism is often cited during the investigation of fatigue.[10] In this study participants with low TSH levels reported fatigue more frequently, but this association was significant only after multivariable analysis with inverse probability weighting. Furthermore, the prevalence of low TSH levels was <1% in the overall sample. The associations between hypothyroidism and fatigue have been controversial for a long time.[10] Basu et al. found no association between TSH categories and fatigue [13] and Canaris et al [47] reported that the association between fatigue and hypothyroidism was weak. Overall, our results suggest that, in presence of fatigue, hypothyroidism is an unlikely cause and should not be systematically assessed.

Implications of the study

Based on our study findings, we propose to focus on specific clinical and biological factors amenable to treatment at an individual level. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea (namely in presence of a patient with obesity) and the presence of depression should be assessed. Hence, lifestyle measures to improve sleep quality and quantity should be preferred to medication.[22] In the case of depression, it will be important to warn patients that antidepressor medication might not necessarily lead into rapid relief of fatigue. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step.

At the population level, preventive measures such as stress management and health promotion like relaxation, time management and cognitive reframing (for example within the work environment) could improve sleep quality, increase self-rated health [48] and consequently reduce fatigue.

Strengths and limitations

This study has several strengths. Firstly, it is one of the few studies assessing the prevalence and the factors associated with fatigue in a population-based sample, which is of interest for public health. Secondly, it explored a large panel of possible factors associated with fatigue, thus allowing the identification of factors significantly and independently associated with fatigue.

This study has also several limitations. Firstly, its cross sectional setting precludes the identification of the causes of fatigue, as reverse causality is possible (i.e. fatigue leading to depression and vice-versa).[3] All participants of the CoLaus study are currently being re-contacted and re-examined, so a prospective analysis of the causes of fatigue will be feasible within two years. Secondly, there is no gold standard for the evaluation of fatigue and no official definition of fatigue. Hence, results might vary according to the scale applied or how participants interpret the term “fatigue”. In this study, we chose to use a scale that was previously applied by other authors to facilitate comparisons. Thirdly, only the German version of the FSS has been validated in Switzerland; the French version used in this study has not yet been validated. Hence, it is possible that the true prevalence levels of fatigue might be under- or over-estimated, or that some items of the questionnaire might not be informative. Still, the Cronbach’s alpha for the questionnaire was 0.918, suggesting an excellent internal consistency. Furthermore, our results provide a first estimation of the prevalence of fatigue in the Swiss French-speaking general population, which could serve as a reference for further studies. Fourthly a sizable fraction of the sample was excluded, both between the baseline and the second follow-up, and within the current study, which might limit the generalizability of the findings. For instance, excluded participants were more frequently women; as women reported more frequently fatigue, this might lead to an underestimation of prevalence rates or a decrease in the strength of the associations. Still, an analysis using a propensity score weighting for the probability of being excluded led to similar findings. Conversely, it was not possible to assess the reasons why participants did not complete the questionnaire. Fifthly,

no information was available regarding shift work or the presence of very young children. Still, as a sizable fraction (almost 70%) of the sample was aged over 55 and over 36% of the sample was aged over 64, it is likely that the number of participants either on shift work or with very young children would be small. Sixthly, the FSS explored fatigue during the previous week while the ISI score explored the sleep during the previous month. Hence, it is possible that the time association between the two variables might not be optimal. Still, as the FSS lies within the period encompassed by the ISI, we believe that the associations obtained are clinically relevant. Seventhly, the study is limited to the population of aged 45 to 86, and its generalizability remains to be assessed. For instance, no information was collected regarding other confounders among younger subjects, where prevalence of fatigue might be higher due to parental and professional duties.[49]. Finally, possible biases related to the self-reporting of fatigue could not be avoided, such as over- or under-estimation of symptoms or misunderstanding of what the term "fatigue" meant; still, this dilution bias would lead to a decrease in the strength of the associations, and it would be too restrictive in our opinion to provide a definition of the term "fatigue" to the participants, as different interpretations of the definition itself could also occur.

Recommendations for future studies

Future studies on the prevalence of fatigue in the general population should focus on the following topics: 1) validate the questionnaires in the population of interest; 2) whenever possible, use a standardised questionnaire to allow comparison between studies.

While some factors such as obesity [13 33], depression [13 39-41] and antidepressor medications [3] were consistently associated with fatigue in our study and in the literature, controversial findings such as the association between fatigue and gender, age groups and anemia should be further explored.

CONCLUSION

In a population-based sample, fatigue was present in one out of five subjects aged 45 to 86. The major factors associated with fatigue were obesity, insomnia, depression, anemia

and antidepressant medication. The results should be interpreted taking into account the high exclusion rate.

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COMPETING INTERESTS

The authors report no competing interests.

AUTHORS' CONTRIBUTION

CG-D conducted the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and wrote part of the manuscript. PV conceived the study and revised the manuscript for important intellectual content. PM-V has full access to the data and is the guarantor of the manuscript. All authors have read and approved this version of the manuscript.

PATIENT CONSENT FORM

Not applicable

DATA SHARING STATEMENT

Non-identifiable individual-level data are available for researchers who seek to answer questions related to health and disease in the context of research projects who meet the criteria for data sharing by research committees. Please follow the instructions at https://www.colaus-psycolaus.ch/ for information on how to submit an application for gaining access to CoLaus data.

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FATIGUE DURANT LA SEMAINE DERNIÈRE

Lisez chaque affirmation et entourez un nombre de 1 à 7 qui semble correspondre à votre état de fatigue durant la semaine dernière.

- Une valeur basse (1) indique que vous n'êtes pas d'accord avec l'affirmation, tandis qu'une valeur haute (7) indique que vous êtes d'accord avec l'affirmation proposée.
- Il est important d'entourer un nombre (1 à 7) pour chaque question.

Durant la semaine passée j'ai trouvé que…	Pas d'accord ⟷ D'accord						
Ma motivation est plus basse quand je suis fatigué (e)	1	2	3	4	5	6	7
Les exercices entrainent une fatigue	1	2	3	4	5	6	7
Je suis facilement fatigué(e)	1	2	3	4	5	6	7
La fatigue interfère avec mon fonctionnement physique	1	2	3	4	5	6	7
La fatigue me cause souvent des problèmes	1	2	3	4	5	6	7
Ma fatigue empêche des activités physiques soutenues	1	2	3	4	5	6	7
La fatigue m'empêche de mener à bien certaines obligations et responsabilités	1	2	3	4	5	6	7
La fatigue est parmi mes 3 symptômes les plus handicapants	1	2	3	4	5	6	7
La fatigue interfère avec mon travail, ma famille ou ma vie sociale	1	2	3	4	5	6	7

	Scores 1 = Strongly Disagree; 7 = Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Index de sévérité de l'insomnie (ISI)

Instructions

Vos réponses doivent correspondre aux expériences que vous avez eues au cours des derniers mois. Répondez s'il vous plaît à toutes les questions.

Antécédents personnels de difficultés de sommeil :

1. Combien d'heures de sommeil dormez-vous lors d'une nuit habituelle ? _____ heures
2. Considérez-vous que vous avez un problème de sommeil actuellement ? OUI NON
3. Utilisez-vous actuellement des médicaments ou autres substances pour vous aider à dormir ? OUI NON
   Si votre réponse est NON aux deux questions précédentes (n° 2 et 3), passez directement à la question n° 14.
4. Veuillez estimer la **SÉVÉRITÉ** actuelle (dernier mois) de vos difficultés de sommeil.
   a. Difficultés d'endormissement :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

   b. Difficulté de maintien du sommeil :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

   c. Réveil trop précoce le matin :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

5. Êtes-vous actuellement **SATISFAIT(E)/INSATISFAIT(E)** de votre sommeil ?

Très Satisfait	Satisfait	Modérément Satisfait	Insatisfait	Très Insatisfait
0	1	2	3	4

6. À quel point considérez-vous que vos difficultés de sommeil **PERTURBENT** votre fonctionnement quotidien (par exemple, fatigue, concentration, mémoire, humeur) ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

7. À quel point considérez-vous que vos difficultés de sommeil sont **REMARQUÉES** par les autres en termes de détérioration de votre qualité de vie ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

8. À quel point êtes-vous **INQUIET(E)/PRÉOCCUPÉ(E)** par vos difficultés actuelles de sommeil ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

9. Depuis combien de temps ressentez-vous des difficultés de sommeil ?
   En mois : (nombre)
   En années : (nombre)

10. Combien de nuits par semaine pensez-vous avoir des (nombre) difficultés de sommeil ?
    Par semaine (nombre)

11. Avez-vous de la difficulté à rester éveillé le jour ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

12. Avez-vous d'autres difficultés de sommeil ? Si oui, veuillez en préciser la nature :
    _____ cauchemars, _____ difficultés à respirer, _____ ronflement, _____ parler dans votre sommeil, _____ marcher dans votre sommeil, _____ mouvements des membres inférieurs.

13. À quel âge, vos difficultés de sommeil ont-elles débuté ? _____ ans
    Veuillez passer à la question n° 15.

14. **Histoire :**
    Avez-vous eu dans le passé des difficultés de sommeil ayant persisté pour plus d'un mois ?
    OUI NON
    Si non, veuillez passer à la question n° 15.
    Si oui, pour quelle durée ? _____ mois _____ années
    Quel âge aviez-vous à ce moment ? _____ ans
    Quelle était la nature de ces difficultés ? _____
    (voir question n° 12).

15. Souffrez-vous actuellement d'un trouble anxieux ou dépressif ?

16. Prenez-vous actuellement un traitement à visée psychologique ?

Score

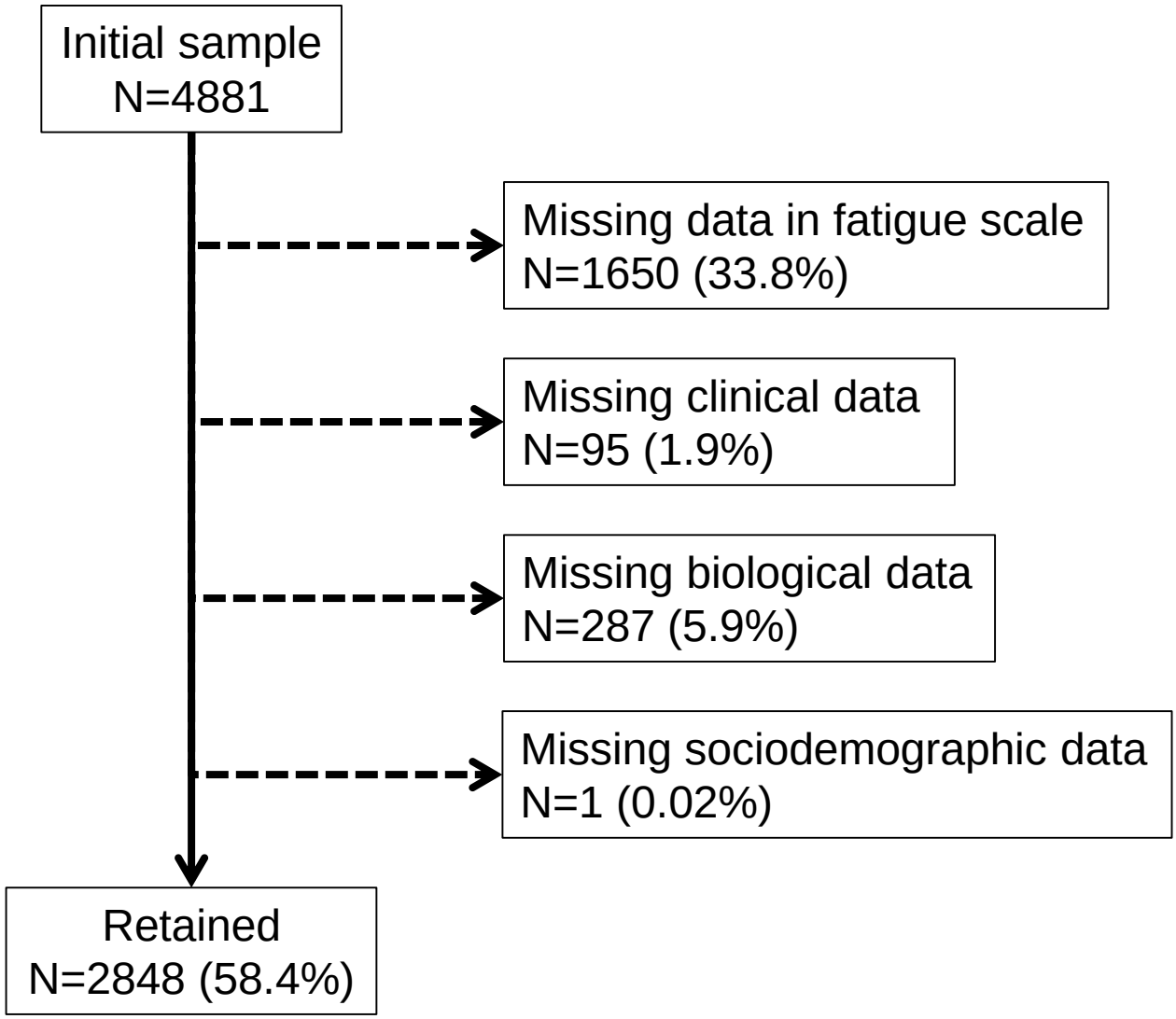
Pour analyser et interpréter ce questionnaire, additionnez les notes données aux questions 4a, 4b, 4c, 5, 6, 7 et 8. Le score total s'établit entre 0 et 28.

0–7	Pas d'insomnie
8–14	Insomnie légère
15–21	Insomnie modérée
22–28	Insomnie sévère

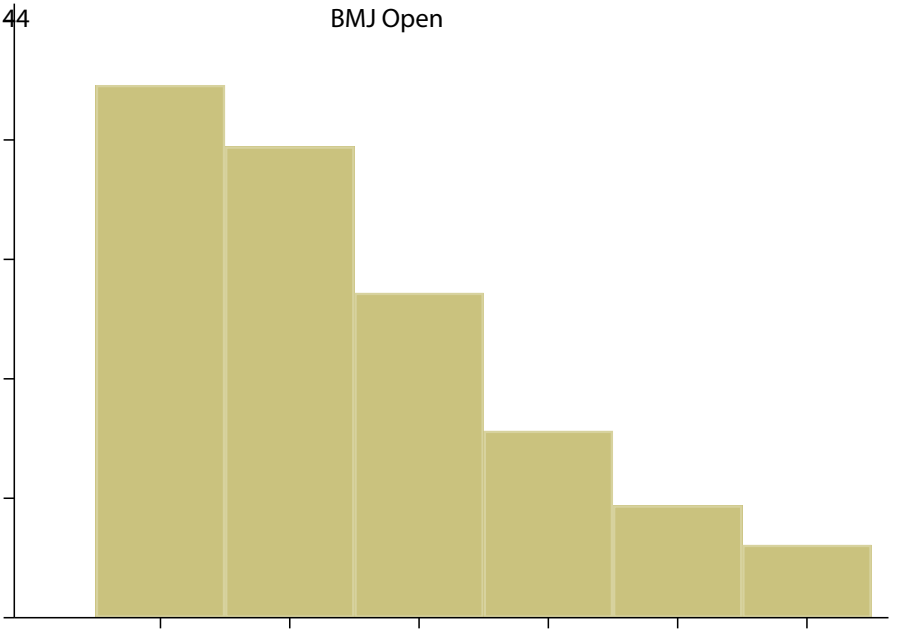
Référence

Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001 ; 2 : 297–307.

Supplemental figure 1: The reasons for exclusion



Exclusion if missing data in fatigue scale, missing clinical, biological and sociodemographic data



Supplemental table 1: comparison between excluded and included participants

	Included	Excluded	p-value
N	2848	2033	
Woman (%)	1514 (53.2)	1175 (57.8)	0.001
Age (years)	61.5 ± 9.8	65.0 ± 11.0	<0.001
Age groups			<0.001
45-54	879 (30.9)	467 (23.0)	
55-64	933 (32.8)	569 (28.0)	
64-74	739 (26.0)	560 (27.6)	
75+	297 (10.4)	437 (21.5)	
Educational level			<0.001
University	683 (24.0)	348 (17.2)	
High school	808 (28.4)	450 (22.2)	
Apprenticeship	1015 (35.6)	734 (36.2)	
Primary	342 (12.0)	497 (24.5)	
Smoking categories			0.015
Never	1149 (41.3)	737 (43.1)	
Former	1130 (40.6)	624 (36.5)	
Current	505 (18.1)	350 (20.5)	
BMI (kg/m^2)	26.4 ± 4.5	26.5 ± 5.0	0.525
BMI categories			0.038
Underweight	42 (1.5)	33 (2.0)	
Normal	1139 (40.0)	643 (39.4)	
Overweight	1157 (40.6)	618 (37.8)	
Obese	510 (17.9)	339 (20.8)	
Caffeinated drinks			<0.001
None	280 (10.1)	182 (11.3)	
1-3/day	1792 (64.7)	1108 (69.0)	
4-6/day	608 (21.9)	272 (16.9)	
7+/day	92 (3.3)	44 (2.7)	
Self-rated health			<0.001
Very good	679 (23.8)	353 (17.8)	
Good	1617 (56.8)	1094 (55.2)	
Average	502 (17.6)	464 (23.4)	
Bad + Very bad	50 (1.8)	72 (3.6)	
Cardiovascular disease	245 (8.6)	274 (13.5)	<0.001
Diabetes	226 (8.0)	256 (15.0)	<0.001
Depression	329 (11.9)	93 (11.9)	0.971
Anemia	109 (3.8)	108 (6.5)	<0.001
Ferritin [mcg/l]	227 [147 - 2.97]	220 [141 - 2.93]	0.058
TSH [mUI/l]	3.0 [2.1 - 3.0]	3.0 [2.1 - 2.9]	0.375
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 3.3	0.534
Anti-hypertensive drugs	885 (31.1)	812 (39.9)	<0.001
Anti-histaminics	68 (2.4)	32 (1.6)	0.048
Antidepressants	278 (9.8)	246 (12.1)	0.009
Hypnotics	122 (4.3)	145 (7.1)	<0.001

BMI, body mass index. Results are expressed as number of participants (column percentage) for categorical variables and as average±standard deviation or median [interquartile range] for continuous variables. Between-group comparison performed using chi-square for categorical variables and using student's t-test or Kruskal-Wallis test (§) for continuous variables.

Supplemental table 2: variables used to compute the propensity score

	Odds ratio (95% CI)	p-value
Gender (woman vs. man)	0.77 (0.64 - 0.93)	0.006
Age groups		
45-54	1 (ref)	
55-64	0.85 (0.68 - 1.07)	0.178
64-74	0.81 (0.63 - 1.03)	0.083
75+	0.50 (0.37 - 0.67)	<0.001
Educational level		
Primary	1 (ref)	
Apprenticeship	1.45 (1.11 - 1.91)	0.007
High school	1.58 (1.19 - 2.10)	0.002
University	1.51 (1.12 - 2.04)	0.007
Smoking categories		
Never	1 (ref)	
Former	1.15 (0.95 - 1.39)	0.155
Current	1.08 (0.85 - 1.39)	0.523
BMI categories		
Underweight	0.80 (0.43 - 1.49)	0.479
Normal	1 (ref)	
Overweight	1.39 (1.14 - 1.69)	0.001
Obese	1.57 (1.20 - 2.05)	0.001
Caffeinated drinks		
None		
1-3/day	1.14 (0.86 - 1.51)	0.369
4-6/day	1.29 (0.93 - 1.78)	0.129
7+/day	1.16 (0.66 - 2.03)	0.599
Self-rated health		
Very good	1 (ref)	
Good	0.98 (0.79 - 1.21)	0.836
Average	1.08 (0.80 - 1.45)	0.610
Bad + Very bad	1.22 (0.55 - 2.73)	0.621
Diabetes (yes vs. no)	0.69 (0.50 - 0.94)	0.021
Anemia (yes vs. no)	0.82 (0.54 - 1.26)	0.369

BMI, body mass index. Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Multivariable analysis performed using logistic regression.

Supplemental table 3: Bivariate and multivariable analysis of the continuous determinants of fatigue as defined by a Fatigue Severity Scale ≥5 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2538	310		2538	310	
Age (years)	61.7 ± 9.8	60.0 ± 10.0	0.005			
BMI (kg/m^2)	26.2 ± 4.4	27.8 ± 5.4	<0.001			
Handgrip (kg)	35.0 ± 12.0	32.8 ± 11.4	0.002	35.1 ± 0.1	35.4 ± 0.5	0.453
Ferritin [mcg/l]	149 [91 - 229]	138 [84 - 208]	0.083 §	185.1 ± 3.5	205.1 ± 11.3	0.098
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 3.0]	1.000 §	2.5 ± 0.1	2.5 ± 0.1	0.987
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 2.6	0.968	16.3 ± 0.1	16.2 ± 0.2	0.881

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, self-rated health and depression.

Supplemental table 4: Bivariate and multivariable analysis of the categorical determinants of fatigue as defined by a Fatigue Severity Scale ≥5 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable model 1		Multivariable model 2	
	No fatigue	**Fatigue**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Gender			0.011				
Man	1210 (47.7)	124 (40.0)		1 (ref)		1 (ref)	
Woman	1328 (52.3)	186 (60.0)		1.45 (1.05 - 1.99)	0.024	1.43 (1.04 - 1.95)	0.027
Age group			<0.001				
45-54	758 (29.9)	121 (39)		1 (ref)		1 (ref)	
55-64	829 (32.7)	104 (33.6)		0.70 (0.49 – 1.00)	0.051	0.70 (0.49 - 0.99)	0.045
64-74	691 (27.2)	48 (15.5)		0.42 (0.27 - 0.64)	<0.001	0.41 (0.26 - 0.63)	<0.001
75+	260 (10.2)	37 (11.9)		0.81 (0.48 - 1.35)	0.416	0.79 (0.48 - 1.32)	0.370
Educational level			0.106				
Primary	293 (11.5)	49 (15.8)		1 (ref)			
Apprenticeship	905 (35.7)	110 (35.5)		1.03 (0.64 - 1.67)	0.902	-	
High school	720 (28.4)	88 (28.4)		1.11 (0.67 - 1.82)	0.687	-	
University	620 (24.4)	63 (20.3)		1.10 (0.65 - 1.86)	0.728	-	
Smoking categories			0.762				
Never	1028 (41.4)	121 (40.2)		-		-	
Former	1002 (40.4)	128 (42.5)		-		-	
Current	453 (18.2)	52 (17.3)		-		-	
BMI categories			<0.001				
Underweight	41 (1.6)	1 (0.3)		0.22 (0.03 - 1.85)	0.162	0.22 (0.03 - 1.85)	0.162
Normal	1032 (40.7)	107 (34.5)		1 (ref)		1 (ref)	
Overweight	1041 (41.0)	116 (37.4)		0.94 (0.66 - 1.34)	0.742	0.94 (0.66 - 1.33)	0.715
Obese	424 (16.7)	86 (27.7)		1.40 (0.93 - 2.08)	0.103	1.38 (0.93 - 2.06)	0.109
Insomnia categories			<0.001				
No insomnia	1972 (84.3)	145 (54.9)		1 (ref)		1 (ref)	
Subthreshold	288 (12.3)	59 (22.4)		1.45 (0.98 - 2.16)	0.064	1.46 (0.98 - 2.15)	0.060
Clinical insomnia	79 (3.4)	60 (22.7)		3.90 (2.41 - 6.33)	<0.001	3.82 (2.36 - 6.18)	<0.001
Caffeinated drinks			0.278				
None	240 (9.7)	40 (13.3)		-		-	

1-3/day	1603 (64.9)	189 (62.8)		-		-	
4-6/day	546 (22.1)	62 (20.6)		-		-	
7+/day	82 (3.3)	10 (3.3)		-		-	
Self-rated health			<0.001				
Very good	656 (25.9)	23 (7.4)		1 (ref)		1 (ref)	
Good	1505 (59.3)	112 (36.1)		1.61 (0.98 - 2.64)	0.062	1.58 (0.96 - 2.60)	0.069
Average	358 (14.1)	144 (46.5)		5.80 (3.40 - 9.87)	<0.001	5.65 (3.34 - 9.58)	<0.001
Bad + Very bad	19 (0.8)	31 (10.0)		17.7 (7.32 - 42.6)	<0.001	17.2 (7.16 - 41.1)	<0.001
Cardiovascular disease			0.617				
No	2322 (91.5)	281 (90.7)		-		-	
Yes	216 (8.5)	29 (9.4)		-		-	
Diabetes			0.006				
No	2343 (92.5)	273 (88.1)		1 (ref)		1 (ref)	
Yes	189 (7.5)	37 (11.9)		0.99 (0.58 - 1.70)	0.975	0.99 (0.58 - 1.69)	0.979
Depression (CES-D)			<0.001				
No	2260 (91.8)	170 (57.4)		1 (ref)		1 (ref)	
Yes	203 (8.2)	126 (42.6)		3.31 (2.28 - 4.79)	<0.001	3.34 (2.31 - 4.83)	<0.001
Anemia			0.325				
No	2444 (96.3)	295 (95.2)		1 (ref)		-	
Yes	94 (3.7)	15 (4.8)		1.24 (0.60 - 2.59)	0.557	-	
Ferritin categories			0.971				
>50	2294 (90.4)	280 (90.3)		-		-	
Normal + low	244 (9.6)	30 (9.7)		-		-	
TSH categories			0.842				
High > 4.22	223 (8.8)	30 (9.7)		1.50 (0.92 - 2.44)	0.105	-	
Normal 0.27-4.22	2294 (90.4)	277 (89.4)		1 (ref)		-	
Low < 0.27	21 (0.8)	3 (1.0)		0.63 (0.13 - 3.11)	0.566	-	
Free T4 categories			0.636				
High > 22	58 (2.3)	6 (1.9)		-		-	
Normal 12-22	2419 (95.3)	294 (94.8)		-		-	
Low < 12	61 (2.4)	10 (3.2)		-		-	
Anti-hypertensive			0.461				
No	1755 (69.2)	208 (67.1)		-		-	

Yes	783 (30.9)	102 (32.9)		-		-	
Anti-histaminics			0.156				
No	2481 (97.8)	299 (96.5)		1 (ref)		-	
Yes	57 (2.3)	11 (3.6)		1.06 (0.47 - 2.42)	0.882	-	
Antidepressants			<0.001				
No	2330 (91.8)	240 (77.4)		1 (ref)		1 (ref)	
Yes	208 (8.2)	70 (22.6)		1.48 (0.97 - 2.25)	0.070	1.46 (0.96 - 2.21)	0.076
Hypnotics			0.004				
No	2439 (96.1)	287 (92.6)		1 (ref)		1 (ref)	
Yes	99 (3.9)	23 (7.4)		0.61 (0.31 - 1.23)	0.167	0.63 (0.31 - 1.26)	0.190

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Two multivariable models were applied: model 1 included all variables significantly ($p<0.05$) associated with fatigue using the threshold of ≥4 of the fatigue severity scale, while model 2 included only the variables significantly ($p<0.05$) associated with fatigue using the threshold of ≥5 of the fatigue severity scale.

Supplemental table 5: Multivariable analysis of the categorical determinants of fatigue (defined as a fatigue severity score ≥4) in the CoLaus study, Lausanne, Switzerland, 2014-2017, using inverse probability weighting.

	OR (95% CI)	P-value
Gender (woman vs. man)	1.26 (0.99 - 1.61)	0.064
Age group		
45-54	1 (ref)	
55-64	0.70 (0.53 - 0.91)	0.009
64-74	0.43 (0.31 - 0.59)	<0.001
75+	0.64 (0.42 - 0.96)	0.031
Educational level		
Primary	1 (ref)	
Apprenticeship	1.02 (0.70 - 1.48)	0.923
High school	1.08 (0.74 - 1.59)	0.678
University	0.94 (0.63 - 1.41)	0.768
BMI categories		
Underweight	0.71 (0.20 - 2.56)	0.598
Normal	1 (ref)	
Overweight	1.03 (0.79 - 1.34)	0.833
Obese	1.44 (1.05 - 1.98)	0.022
Insomnia categories		
No insomnia	1 (ref)	
Subthreshold	1.57 (1.15 - 2.14)	0.004
Clinical insomnia	3.74 (2.29 - 6.10)	<0.001
Self-rated health		
Very good	1 (ref)	
Good	1.92 (1.37 - 2.69)	<0.001
Average	5.51 (3.71 - 8.17)	<0.001
Bad + Very bad	17.2 (7.51 - 39.3)	<0.001
Diabetes (yes vs. no)	1.15 (0.76 - 1.74)	0.501
Depression (CES-D, yes vs. no)	3.21 (2.34 - 4.42)	<0.001
Anemia (yes vs. no)	1.58 (0.91 - 2.76)	0.107
TSH categories		
High > 4.22	1.15 (0.77 - 1.70)	0.499
Normal 0.27-4.22	1 (ref)	
Low < 0.27	3.30 (1.09 - 10.0)	0.035
Anti-histaminics (yes vs. no)	1.33 (0.69 - 2.57)	0.398
Antidepressants (yes vs. no)	1.39 (0.98 - 1.97)	0.069
Hypnotics (yes vs. no)	0.59 (0.31 - 1.10)	0.098

Results are expressed as multivariable-adjusted odds ratio (OR) and (95% confidence interval - CI). Multivariable analysis performed using logistic regression with inverse probability weighting.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Suppl figure 1
		(b) Give reasons for non-participation at each stage	Suppl figure 1
		(c) Consider use of a flow diagram	Suppl figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl table 1

		(b) Indicate number of participants with missing data for each variable of interest	Suppl figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl table 2-3-4-5
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

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Prevalence and factors associated with fatigue in the Lausanne middle-aged population: A population based cross-sectional survey

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Prevalence and factors associated with fatigue in the Lausanne middle-aged population: A population based cross-sectional survey

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Abstract

Objective: To assess the prevalence and factors associated with fatigue in the general population.

Design: Population based cross-sectional survey performed between May 2014 and April 2017.

Setting: General population of the city of Lausanne, Switzerland.

Participants: 2848 participants (53.2% women, age range 45-86 years).

Primary outcome measure: Prevalence of fatigue the previous week, defined as a score ≥4 using the Fatigue Severity Scale (FSS).

Results: The prevalence of fatigue was 21.9% (95% CI: 20.4% – 23.4%) in the total sample. On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels. Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression, low TSH values, had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad. Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated with fatigue; while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics.

Conclusion: In a population-based sample aged 45 to 86, fatigue was present in one out of five subjects. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea should be assessed first, followed by depression. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step. Sleep complaints and fatigue in older subjects are not due to aging and should prompt the identification of the underlying cause.

Keywords: fatigue; prevalence; epidemiology; Fatigue severity scale

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study assessed the prevalence and factors associated with fatigue in a general population setting.
- A large panel of associated with fatigue was evaluated.
- A list of the most frequent determinants was established, facilitating etiological search in clinical practice
- The study was limited to subjects aged 45 to 86, so results do not apply to younger or older groups.

INTRODUCTION

Fatigue is usually defined as "an unpleasant physical, cognitive and emotional symptom described as a tiredness not relieved by common strategies that restore energy".[1] Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities. [1] Indeed, fatigue is a common symptom with prevalence rates varying between 4 and 45%. [2-4] This ten-fold range in prevalence rates is likely due to the different settings (i.e. general practice [5] or workers [6]) or the different methods used to assess fatigue. [7]

In healthy subjects, tiredness or sleepiness are a natural occurrence after physical or mental efforts, and are usually relieved by rest. [8 9] While fatigue is defined as extreme and persistent tiredness, weakness or exhaustion, of mental and/or physical origin [7] that is not relieved by rest. Fatigue is defined in duration as recent (<1 month) prolonged (1 to 6 months) and chronic (>6 months) [10]. When unexplained, chronic fatigue can be considered either as a syndrome (characterized by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches) [11] or as idiopathic (absence of other symptoms).

Fatigue is one of the most common complaints reported in primary care [12] and is associated with a decreased quality of life and increased morbidity and mortality in the general population. [13] Fatigue is a multidimensional concept, and several determinants have been proposed. Although a cause (somatic or psychiatric) is identifiable in 2/3 of fatigue cases, 1/3 of fatigue cases still have no specific diagnosis.[10] The most frequent diagnoses associated with fatigue are viral or upper respiratory tract infection, iron deficiency anemia, adverse effects of medication, depression or other mental disorders.[14] Fatigue has also been associated with female sex, [8 15] older age [16 17] and lower socioeconomic status, [16 17] although the association with the last two determinants were not found in some studies. [8 18] Importantly, most studies on fatigue have been conducted in selected populations such as workers [6] or general practice attendees.[2 5 18] To our knowledge, only two studies have assessed the prevalence of fatigue in the general population [8 19] and only a few have explored the

determinants of fatigue in the general population.[13 15-17 20 21] Furthermore, most studies focused on socio-economic and disease determinants of fatigue, while information regarding the biological determinants (i.e. anemia or thyroid pathology) [13] or the medications associated with fatigue is scarce. Moreover, to date, little is known about the prevalence of fatigue and its determinants in Switzerland.

Hence, this study aimed to examine the prevalence and the factors associated with fatigue in a population-based sample from the city of Lausanne, Switzerland.

POPULATION AND METHODS

Study population

The CoLaus study is a population-based cohort exploring biological, genetic, and environmental determinants of cardiovascular diseases. Detailed descriptions of the study design have been reported elsewhere.[22] Briefly, a non-stratified random representative sample of the population of Lausanne was recruited between 2003 and 2006 using the following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate. The first follow-up was performed between April 2009 and September 2012 and the second follow-up between May 2014 and April 2017, 10.9 years on average after the baseline study. At both baseline and subsequent follow-ups, participants were invited to attend a clinical examination at the Lausanne university hospital. Participants received a paper questionnaire at home, which they filled prior to the clinical examination. During the clinical examination, a second questionnaire regarding personal and family history of cardiovascular disease and cardiovascular risk factors was applied. For more details, please consult www.colaus-psycolaus.ch.

As fatigue was only assessed in the second follow-up, data from the second follow-up, which included 4881 of the initial 6773 participants recruited at baseline, was used. At the second follow-up, participants were aged 45-86 years.

Fatigue scale

Fatigue severity during the previous week was assessed by the 9 items Fatigue Severity Scale (FSS). [9] The FSS is one of the most commonly used fatigue questionnaires. It had been validated in a healthy population setting in German-speaking Switzerland [23], Portugal [24] and Norway [19]. It is a simple, time-saving, self-administrated questionnaire allowing its use in large epidemiological studies and has a high test-retest reliability. [7] The questionnaire is composed of nine questions; responses are graded using a Likert scale from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement. The final score is the mean value of the nine responses, and a score ≥4 is considered as having severe fatigue. This cutoff was initially proposed because <5% of healthy controls rate their fatigue at that level, whereas 60-90% of patients with medical disorders experience fatigue at or above this level. [9] An example of the questionnaire in French is provided in **Annex 1,** in English in **Annex 2**. To our knowledge, the French version of the FSS has not yet been validated in Switzerland. Still, the Cronbach's alpha for the questionnaire was 0.918, suggesting an excellent internal consistency.

Covariates

Socioeconomic and lifestyle variables were collected using a self-administered questionnaire. Smoking status was categorized into never, former and current smoker. Educational level was collected at baseline and categorized as obligatory school, apprenticeship, high school/college or university.

Insomnia was assessed using the Insomnia Severity Index (ISI).[25] The questionnaire has 16 items evaluating the nature, severity, and impact of insomnia over the last month; namely difficulties falling asleep, sleep maintenance problems, and early morning awakening, sleep dissatisfaction, interference of sleep disturbances with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Responses range from 0 "Not at all" to 4 "Extremely". Items were scaled 0-4 and then summed to obtain the global ISI score (range: 0-28). The questionnaire is provided in **Annex 3** in French and in

Annex 4 in English. Clinically significant insomnia was defined as an ISI score ≥15 (moderate to severe intensity).[25]

Depression was assessed with the CES-D [26], a 20 item self-report instrument, developed for research in the general population, that is used to assess the severity of depressive symptoms over the past week on a 4-point scale. It was translated into French by Fuhrer and Rouillon.[27] It has been used in other recent epidemiological studies assessing the link between depression and cardiovascular risk factors [28]. The questionnaire is composed of 20 questions; responses are graded from 0 to 3, where 0 indicates rarely or never (less than one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the 20 responses (possible range is 0-60), and a score ≥16 is considered as a risk for depression.

Self-rated health was assessed by a single question where participants had to rate their current health status from five categories ranging from “very bad” to “very good”. As the number of participants rating their health as “very bad” was very small, they were grouped with the participants who rated their health as “bad”.

Body weight and height were measured with participants standing without shoes in light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as weight/height^2 and categorized as underweight (BMI<18.5 kg/m^2), normal (18.5≤BMI<25 kg/m^2); overweight (25≤ BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2).

Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and 30° of dorsiflexion. Three measurements were performed consecutively with the right hand and the highest value (expressed in kg) was included in the analyses.

Caffeinated drink consumption was assessed by the question “How many cups or cans of drinks containing caffeine (coffee, tea, coke or similar) do you drink per day?” with possible answers “None”, “1-3”, “4-6” and “7 or more”.

Participants were asked to report all medications (prescribed or bought over the counter) they took during the last 6 months. Medications were coded using the Anatomical, Therapeutic Chemical (ATC) classification of the world health organization (www.whocc.no/atc_ddd_index/). Antihistamics were defined as any ATC code beginning with “R06”; antidepressants were defined as an ATC code beginning with “N05BD" or N06AA" or “N06AB" or “N06AF" or “N06AG" or “N06AX" or “N06CA"; hypnotics were defined as any ATC code beginning with “N05C”. Antihypertensive drugs were defined by asking the participants if they were taking drugs for hypertension.

Diabetes was defined by a fasting plasma glucose ≥7 mmol/L and/or the presence of an antidiabetic drug treatment (oral or insulin). Personal history of cardio vascular disease was assessed by asking the participant if he/she had sustained a coronary event (myocardial infarction or angina pectoris) or a stroke.

Biological assays were performed by the CHUV Clinical Laboratory on fresh blood samples within 2 hours of blood collection, and additional aliquots were stored at –80°C. All measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland). The following analytical procedures (with maximum inter and intra-batch CVs) were used: high sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by immunoturbidimetric method (Tina-quant 4th generation, Roche Diagnostics, Switzerland) with a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid stimulating hormone (TSH) and free T_4 were assessed by chemiluminescence (ECLIA) on a Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free T_4.

Exclusion criteria

Participants were excluded if they lacked 1) any answer to the fatigue questionnaire; 2) clinical data such as age, body mass index, smoking, depression, insomnia or medications; 3) biological measures such as haemoglobin or thyroid hormones and 4) socioeconomic data such as educational level.

Ethical statement and consent

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-up. The full decisions of the CER-VD can be obtained from the authors upon request. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Patient and Public Involvement

No patients or public were involved in this study design, conduct or analysis.

Statistical analysis

Statistical analysis was performed using Stata version 15.1 for windows (Stata Corp, College Station, Texas, USA). Prevalence rates for fatigue were expressed as percentage and 95% confidence interval (CI). Descriptive results were expressed as number of participants (percentage) for categorical variables or as average±standard deviation for continuous variables. Bivariate analyses were performed using chi-square or Fisher's exact test for categorical variables and student's t-test or Kruskal-Wallis test for continuous variables. All categorical variables significantly ($p<0.05$) associated with fatigue in the bivariate analysis were included in the multivariable analysis. Multivariable analysis was performed using analysis of variance or logistic regression with fatigue (dichotomized into yes/no) as dependent variable; results were expressed as multivariable-adjusted mean±standard error for continuous variables or as Odds ratio (OR) and 95% CI for categorical variables.

Sensitivity analyses were conducted using a FSS threshold of 5. Further, as the number of excluded participants was high, other sensitivity analyses were conducted by creating a propensity score for being excluded [29]. The propensity score was computed using logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly associated with exclusion as independent variables. A probability of exclusion was computed for each participant, and the inverse of the probability was used for weighting.

Statistical significance was assessed for a two-sided test with $p<0.05$.

Results

Study population

Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most frequent reason was lack of data regarding fatigue. The comparison between included and excluded participants is provided in **supplemental table 1** and the results of the multivariable analysis are provided in **supplemental table 2**. Excluded participants were more frequently women, were older, had a lower educational level, were more frequently never or current smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and hypertension) and rated their health worse.

Prevalence and factors associated with fatigue

The overall prevalence of fatigue as defined by a FSS ≥4 was 21.9% (95% CI: 20.4% – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% - 22.3%), p=0.031. The distribution of the FSS ≥5 (prevalence of fatigue 10.9%) is provided in **supplemental figure 2**; the number of participants with fatigue decreased when the levels of FSS increased.

The analysis of the factors associated with fatigue as defined by a FSS ≥4 is provided in **Tables 1 and 2**.

Table 1: Bivariate and multivariable analysis of the continuous factors associated with fatigue as defined by a Fatigue Severity Scale ≥4 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2225	623				
Age (years)	61.9 ± 9.8	60.0 ± 9.8	<0.001	-	-	
BMI (kg/m^2)	26.1 ± 4.4	27.4 ± 5.0	<0.001	-	-	
Handgrip (kg)	35.0 ± 12.0	33.8 ± 12.0	0.022	35.0 ± 0.2	35.3 ± 0.3	0.430
Ferritin [mcg/l]	149 [92-229]	139 [83-214]	0.034 §	188 ± 4	185 ± 8	0.732
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 2.9]	0.374 §	2.5 ± 0.1	2.4 ± 0.1	0.332
Free T4 [pmol/l]	16.2 ± 2.5	16.3 ± 2.6	0.190	16.2 ± 0.1	16.4 ± 0.1	0.221

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, self-rated health and depression.

Table 2: Bivariate and multivariable analysis of the categorical factors associated with fatigue as defined by a Fatigue Severity Scale ≥4 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable	
	No fatigue	**Fatigue**	**p-value**	**OR (95% CI)**	**p-value**
Gender			0.031		
Man	1066 (47.9)	268 (43.0)		1 (ref)	
Woman	1159 (52.1)	355 (57.0)		1.25 (0.99 - 1.58)	0.065
Age group			<0.001		
45-54	643 (28.9)	236 (37.9)		1 (ref)	
55-64	724 (32.5)	209 (33.6)		0.69 (0.53 - 0.90)	0.006
64-74	626 (28.1)	113 (18.1)		0.43 (0.31 - 0.59)	<0.001
75+	232 (10.4)	65 (10.4)		0.60 (0.40 - 0.90)	0.013
Educational level			0.017		
Primary	249 (11.2)	93 (14.9)		1 (ref)	
Apprenticeship	794 (35.7)	221 (35.5)		1.05 (0.73 - 1.51)	0.782
High school	626 (28.1)	182 (29.2)		1.13 (0.78 - 1.64)	0.520
University	556 (25.0)	127 (20.4)		0.98 (0.66 - 1.46)	0.937
Smoking categories			0.279		
Never	907 (41.7)	242 (39.7)		-	
Former	866 (39.8)	264 (43.4)		-	
Current	402 (18.5)	103 (16.9)		-	
BMI categories			<0.001		
Underweight	37 (1.7)	5 (0.8)		0.69 (0.24 - 2.01)	0.495
Normal	920 (41.4)	219 (35.2)		1 (ref)	
Overweight	914 (41.1)	243 (39.0)		1.01 (0.78 - 1.31)	0.942
Obese	354 (15.9)	156 (25.0)		1.40 (1.03 - 1.91)	0.032
Insomnia categories			<0.001		
No insomnia	1782 (86.2)	335 (62.6)		1 (ref)	
Subthreshold	233 (11.3)	114 (21.3)		1.57 (1.16 - 2.13)	0.003
Clinical insomnia	53 (2.6)	86 (16.1)		3.76 (2.41 - 5.86)	<0.001
Caffeinated drinks			0.147		
None	205 (9.5)	75 (12.3)		-	
1-3/day	1418 (65.5)	374 (61.5)		-	
4-6/day	471 (21.8)	137 (22.5)		-	
7+/day	70 (3.2)	22 (3.6)		-	
Self-rated health			<0.001		
Very good	621 (27.9)	58 (9.3)		1 (ref)	
Good	1323 (59.5)	294 (47.2)		1.94 (1.39 - 2.71)	<0.001
Average	270 (12.1)	232 (37.2)		5.55 (3.78 - 8.14)	<0.001
Bad + Very bad	11 (0.5)	39 (6.3)		14.1 (5.95 - 33.4)	<0.001
Cardiovascular disease			0.697		
No	2036 (91.5)	567 (91.0)		-	
Yes	189 (8.5)	56 (9.0)		-	
Diabetes			<0.001		
No	2069 (93.2)	547 (87.9)		1 (ref)	
Yes	151 (6.8)	75 (12.1)		1.24 (0.82 - 1.87)	0.306
Depression (CES-D)			<0.001		
No	2026 (93.8)	404 (67.6)		1 (ref)	
Yes	135 (6.3)	194 (32.4)		3.26 (2.38 - 4.46)	<0.001

Anemia			0.008		
No	2151 (96.7)	588 (94.4)		1 (ref)	
Yes	74 (3.3)	35 (5.6)		1.70 (1.00 - 2.89)	0.049
Ferritin categories			0.436		
>50	2016 (90.6)	558 (89.6)		-	
Normal + low	209 (9.4)	65 (10.4)		-	
TSH categories			0.017		
High > 4.22	197 (8.9)	56 (9.0)		1.13 (0.77 - 1.66)	0.533
Normal 0.27-4.22	2015 (90.6)	556 (89.3)		1 (ref)	
Low < 0.27	13 (0.6)	11 (1.8)		2.50 (0.91 - 6.85)	0.075
Free T4 categories			0.651		
High > 22	47 (2.1)	17 (2.7)		-	
Normal 12-22	2122 (95.4)	591 (94.9)		-	
Low < 12	56 (2.5)	15 (2.4)		-	
Anti-hypertensive			0.108		
No	1550 (69.7)	413 (66.3)		-	
Yes	675 (30.3)	210 (33.7)		-	
Anti-histaminics			0.007		
No	2181 (98)	599 (96.2)		1 (ref)	
Yes	44 (2.0)	24 (3.9)		1.30 (0.69 - 2.46)	0.417
Antidepressants			<0.001		
No	2062 (92.7)	508 (81.5)		1 (ref)	
Yes	163 (7.3)	115 (18.5)		1.44 (1.02 - 2.04)	0.040
Hypnotics			<0.001		
No	2146 (96.5)	580 (93.1)		1 (ref)	
Yes	79 (3.6)	43 (6.9)		0.57 (0.32 - 1.03)	0.062

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Only variables with p<0.05 in the bivariate analysis were retained for the multivariable analysis.

On bivariate analysis, participants with fatigue were younger, had a higher BMI, a lower handgrip strength, and lower ferritin levels (**Table 1**). Participants with fatigue were more frequently women, had a lower educational level, and presented more frequently with clinical insomnia, diabetes, anemia, depression and low TSH values (**Table 2**). Finally, participants with fatigue had a higher consumption of anti-histaminics, antidepressants and hypnotics, and rated more frequently their health as bad or very bad (**Table 2**).

Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26

(2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-histaminics or hypnotics (**Table 2**).

Sensitivity analyses

The overall prevalence of fatigue as defined by a FSS ≥5 was 10.9% (95% CI: 9.7% – 12.1%) and was higher in women 12.3% (10.7% - 14.0%) than in men 9.3% (7.8% - 11.1%), p=0.011. The results of the sensitivity analyses using a FSS threshold of ≥5 are provided in **supplemental tables 3 and 4**. Overall, the results were comparable with those using a threshold of ≥4: gender, insomnia categories (p-value for trend <0.001), and low self-rated health status (p-value for trend <0.001) were positively associated with fatigue. Conversely, no association was found for age, obesity, diabetes, TSH levels, antihistaminics, antidepressives or hypnotics (**supplemental table 4**).

Sensitivity analysis using inverse probability weighting by the propensity score led to similar findings, except that anemia and antidepressants were no longer associated with fatigue, while a positive association was found between low TSH levels and fatigue (**Supplemental table 5**).

Discussion

To our knowledge, this is one of the few studies assessing the prevalence and the factors associated with fatigue in a general population setting, and the first study conducted in Switzerland. Using a FSS cut-off ≥4, our results indicate that one out of five people aged between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and decreasing self-rated health status were positively associated with fatigue; while older age was negatively associated with fatigue.

Prevalence of fatigue

Using the cut-off of ≥4, fatigue was present in one out of five participants (22.1%), a finding in agreement with the study by Loge et al. [8], which reported a prevalence of 22% among 2323 participants using the Chalder fatigue scale. Conversely, the cross-sectional study by Lerdal et al. [19], which used the FSS in a sample of 1893 participants, reported a prevalence of fatigue of 46.7% and 23.1% using a cut-off of ≥4 and ≥5 respectively, in comparison 22.1% and 10.9% in our study). The investigated population was aged 19-81 years, included younger patients (women of childbearing age with menstruation and young parents) compared to our study aged between 45 and 86 years; that could explain this difference in prevalence of fatigue. A study conducted in general practice reported a prevalence of fatigue of 38% using the Chalder fatigue scale,[2] whereas a study conducted in the Dutch working population reported a prevalence of fatigue of 22% using other fatigue measures. [6] Comparison between studies is hampered by the small number of studies assessing the prevalence of fatigue in non-selected samples, the different fatigue scales used and the somewhat different settings (i.e. general population vs. general practice). Still, they provide a first basis for comparison, and it would be important that future studies use similar assessment methods to facilitate comparisons. Overall, our results suggest that the prevalence of fatigue in the Lausanne population is comparable or lower than reported previously.

Clinical and societal factors associated with fatigue

Women tended to report fatigue more frequently than men, but this association was no longer significant after multivariable adjustment. Higher prevalence of fatigue in women has been found in some studies [8 15] but not in others.[18] In a Swedish study conducted in 2014, Engberg et al. [16] considered that this difference could be due to factors related to gender inequalities regarding household responsibilities and child raising, as the gender gap in general fatigue was largest among those aged <55 years.

Younger people reported fatigue more frequently than elderly, a finding in agreement with a Swedish study conducted in 2014. [16] Similarly, a previous study found that older subjects complain less of sleepiness. [30] Still, this association was no longer statistically significant when the cut off of ≥5 was applied to define fatigue, suggesting that young subjects tend to present with borderline fatigue as suggested previously [19]. Conversely, earlier studies (1990-2000) found a positive association between age and fatigue.[8] [17] [21] A possible explanation for this difference is that older people might have a better quality of life nowadays and are less depressed. Although there is little information regarding trends in quality of life among Swiss elderly, the VLV study [31] concluded that quality of life among Swiss elderly increased in the last 30 years [32]. Indeed, in our study, the lowest prevalence of fatigue was reported by participants aged 64-74 years, which are the "young" retired with few comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and 12.5% in the 45-54 and 55-64 years, respectively, p-value<0.001).

Obese subjects had a higher prevalence of fatigue defined by a FSS ≥4. This finding is in agreement with studies conducted in the USA [33] and in the UK.[13] . Still, this association was no longer statistically significant when the cut off of ≥5 was applied to define fatigue, suggesting that obese subjects tend to present with borderline fatigue as suggested previously [19]. Obesity is a risk factor for sleep apnoea, which leads to increased daytime sleepiness. Still, the association persisted after adjusting for insomnia, a finding in agreement with a previous study that showed that obese subjects have excessive fatigue independently of sleep-disordered breathing.[34] Because it excluded too much subjects, we did not correlate obesity and sleep-disordered breathing in our study. A possible explanation could be the increase in proinflammatory cytokines in obese subjects,[35] which would lead to higher fatigue,[36] but other factors such as decreased physical fitness should be further explored.

A positive association was found between self-reported clinical insomnia and fatigue, and this association was independent of obesity, depression and antidepressant medication.

Fatigue is a core symptom of insomnia [34] and a Norwegian study conducted in 2014 showed that reducing insomnia severity led to a concomitant reduction in fatigue.[37] Interestingly, many subjects with sleep complaints do not consult for this issue,[38] which might lead to an underestimation of its prevalence. Overall, our results suggest that insomnia is an important and underestimated factor of fatigue.

Both depression and antidepressant medication were independently and positively associated with fatigue. The association between depression and fatigue has been repeatedly reported,[13 39-41] and the same applies for antidepressant medication.[3] Our results confirm the known association between depression and fatigue, and suggest that antidepressant treatment might not systematically relieve fatigue among depressive subjects. Furthermore, fatigue is a common side effect of antidepressant therapy and a symptom of depression, making the identification of the cause of fatigue difficult with a possibility of reverse causality (fatigue leading to depression and vice versa). We used a one-dimensional tool to evaluate fatigue (FSS); hence, we cannot distinguish between physical and mental fatigue. There is considerable overlap in phenomenology of fatigue and depression or anxiety but there are some important differences. People with fatigue without psychiatric symptoms tend to attribute their symptoms to external causes. Conversely, most depressed people experience self-blame or lowered self-esteem [42]. Further, fatigue and depression commonly appear together. A study conducted in 2009 by Harvey et al. [43], showed that 7% of fatigued persons have no psychiatric symptoms, but remained at increased risk of later psychiatric disorder independently of the severity of fatigue.

A strong association was found between poor self-rated health and fatigue, a finding also reported elsewhere.[6 16] Low self-rated health has been associated with increased levels of inflammatory markers such as interleukin 6 and CRP,[44] which in turn could trigger fatigue. Conversely, increased fatigue might lead to a lower rating of health status.

Biological factors associated with fatigue

Participants with anemia had a higher likelihood of reporting fatigue. This finding is in agreement with the literature,[45] [46] although no association between fatigue and low haemoglobin levels was found in a UK study. [13] A possible explanation is that in the UK study, anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds used in our study (<133 g/l for men and <117 g/l for women). This led to a small sample size (356 participants, corresponding to 1.9% of the overall sample) and thus a low statistical power.

Hypothyroidism is often cited during the investigation of fatigue.[10] In this study participants with low TSH levels reported fatigue more frequently, but this association was significant only after multivariable analysis with inverse probability weighting. Furthermore, the prevalence of low TSH levels was <1% in the overall sample. The associations between hypothyroidism and fatigue have been controversial for a long time.[10] Basu et al. found no association between TSH categories and fatigue [13] and Canaris et al [47] reported that the association between fatigue and hypothyroidism was weak. Overall, our results suggest that, in presence of fatigue, hypothyroidism is an unlikely cause and should not be systematically assessed.

Implications of the study

Based on our study findings, we propose to focus on specific clinical and biological factors amenable to treatment at an individual level. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea (namely in presence of a patient with obesity) and the presence of depression should be assessed. Hence, lifestyle measures to improve sleep quality and quantity should be preferred to medication.[22] In the case of depression, it will be important to warn patients that antidepressor medication might not necessarily lead into rapid relief of fatigue. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step.

At the population level, preventive measures such as stress management and health promotion like relaxation, time management and cognitive reframing (for example within the

work environment) could improve sleep quality, increase self-rated health [48] and consequently reduce fatigue.

Strengths and limitations

This study has several strengths. Firstly, it is one of the few studies assessing the prevalence and the factors associated with fatigue in a population-based sample, which is of interest for public health. Secondly, it explored a large panel of possible factors associated with fatigue, thus allowing the identification of factors significantly and independently associated with fatigue.

This study has also several limitations. Firstly, its cross sectional setting precludes the identification of the causes of fatigue, as reverse causality is possible (i.e. fatigue leading to depression and vice-versa).[3] All participants of the CoLaus study are currently being re-contacted and re-examined, so a prospective analysis of the causes of fatigue will be feasible within two years. Secondly, there is no gold standard for the evaluation of fatigue and no official definition of fatigue. Hence, results might vary according to the scale applied or how participants interpret the term “fatigue”. In this study, we chose to use a scale that was previously applied by other authors to facilitate comparisons. Thirdly, only the German version of the FSS has been validated in Switzerland; the French version used in this study has not yet been validated. Hence, it is possible that the true prevalence levels of fatigue might be under- or over-estimated, or that some items of the questionnaire might not be informative. Still, the Cronbach’s alpha for the questionnaire was 0.918, suggesting an excellent internal consistency. Furthermore, our results provide a first estimation of the prevalence of fatigue in the Swiss French-speaking general population, which could serve as a reference for further studies. Fourthly a sizable fraction of the sample was excluded, both between the baseline and the second follow-up, and within the current study, which might limit the generalizability of the findings. For instance, excluded participants were more frequently women; as women reported more frequently fatigue, this might lead to an underestimation of prevalence rates or

a decrease in the strength of the associations. Still, an analysis using a propensity score weighting for the probability of being excluded led to similar findings. Conversely, it was not possible to assess the reasons why participants did not complete the questionnaire. Fifthly, no information was available regarding shift work or the presence of very young children. Still, as a sizable fraction (almost 70%) of the sample was aged over 55 and over 36% of the sample was aged over 64, it is likely that the number of participants either on shift work or with very young children would be small. Sixthly, the FSS explored fatigue during the previous week while the ISI score explored the sleep during the previous month. Hence, it is possible that the time association between the two variables might not be optimal. Still, as the FSS lies within the period encompassed by the ISI, we believe that the associations obtained are clinically relevant. Seventhly, the study is limited to the population of aged 45 to 86, and its generalizability remains to be assessed. For instance, no information was collected regarding other confounders among younger subjects, where prevalence of fatigue might be higher due to parental and professional duties.[49]. Finally, possible biases related to the self-reporting of fatigue could not be avoided, such as over- or under-estimation of symptoms or misunderstanding of what the term “fatigue” meant; still, this dilution bias would lead to a decrease in the strength of the associations, and it would be too restrictive in our opinion to provide a definition of the term “fatigue” to the participants, as different interpretations of the definition itself could also occur.

Recommendations for future studies

Future studies on the prevalence of fatigue in the general population should focus on the following topics: 1) validate the questionnaires in the population of interest; 2) whenever possible, use a standardised questionnaire to allow comparison between studies.

While some factors such as obesity [13 33], depression [13 39-41] and antidepressor medications [3] were consistently associated with fatigue in our study and in the literature, controversial findings such as the association between fatigue and gender, age groups and anemia should be further explored.

CONCLUSION

In a population-based sample aged 45 to 86, fatigue was present in one out of five subjects. Regarding clinical factors, sleep disturbances such as insomnia and sleep apnea should be assessed first, followed by depression. Regarding biological factors, anemia should be ruled out, while screening for hypothyroidism is not recommended as a first step. Sleep complaints and fatigue in older subjects are not due to aging and should prompt the identification of the underlying cause.

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COMPETING INTERESTS

The authors report no competing interests.

AUTHORS' CONTRIBUTION

CG-D conducted the literature search, interpreted the results and wrote the manuscript. PM-V performed the statistical analyses and wrote part of the manuscript. PV conceived the study and revised the manuscript for important intellectual content. PM-V has full access to the data and is the guarantor of the manuscript. All authors have read and approved this version of the manuscript.

PATIENT CONSENT FORM

Not applicable

DATA SHARING STATEMENT

Non-identifiable individual-level data are available for researchers who seek to answer questions related to health and disease in the context of research projects who meet the criteria for data sharing by research committees. Please follow the instructions at https://www.colaus-psycolaus.ch/ for information on how to submit an application for gaining access to CoLaus data.

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FATIGUE DURANT LA SEMAINE DERNIÈRE

Lisez chaque affirmation et entourez un nombre de 1 à 7 qui semble correspondre à votre état de fatigue durant la semaine dernière.

- Une valeur basse (1) indique que vous n'êtes pas d'accord avec l'affirmation, tandis qu'une valeur haute (7) indique que vous êtes d'accord avec l'affirmation proposée.
- Il est important d'entourer un nombre (1 à 7) pour chaque question.

Durant la semaine passée j'ai trouvé que…	Pas d'accord ⟷ D'accord						
Ma motivation est plus basse quand je suis fatigué (e)	1	2	3	4	5	6	7
Les exercices entrainent une fatigue	1	2	3	4	5	6	7
Je suis facilement fatigué(e)	1	2	3	4	5	6	7
La fatigue interfère avec mon fonctionnement physique	1	2	3	4	5	6	7
La fatigue me cause souvent des problèmes	1	2	3	4	5	6	7
Ma fatigue empêche des activités physiques soutenues	1	2	3	4	5	6	7
La fatigue m'empêche de mener à bien certaines obligations et responsabilités	1	2	3	4	5	6	7
La fatigue est parmi mes 3 symptômes les plus handicapants	1	2	3	4	5	6	7
La fatigue interfère avec mon travail, ma famille ou ma vie sociale	1	2	3	4	5	6	7

	Scores 1 = Strongly Disagree; 7 = Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Index de sévérité de l'insomnie (ISI)

Instructions

Vos réponses doivent correspondre aux expériences que vous avez eues au cours des derniers mois. Répondez s'il vous plaît à toutes les questions.

Antécédents personnels de difficultés de sommeil :

1. Combien d'heures de sommeil dormez-vous lors d'une nuit habituelle ? _____ heures
2. Considérez-vous que vous avez un problème de sommeil actuellement ? OUI NON
3. Utilisez-vous actuellement des médicaments ou autres substances pour vous aider à dormir ? OUI NON
   Si votre réponse est NON aux deux questions précédentes (n° 2 et 3), passez directement à la question n° 14.
4. Veuillez estimer la **SÉVÉRITÉ** actuelle (dernier mois) de vos difficultés de sommeil.
   a. Difficultés d'endormissement :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

   b. Difficulté de maintien du sommeil :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

   c. Réveil trop précoce le matin :

Aucune	Légère	Modérée	Sévère	Très sévère
0	1	2	3	4

5. Êtes-vous actuellement **SATISFAIT(E)/INSATISFAIT(E)** de votre sommeil ?

Très Satisfait	Satisfait	Modérément Satisfait	Insatisfait	Très Insatisfait
0	1	2	3	4

6. À quel point considérez-vous que vos difficultés de sommeil **PERTURBENT** votre fonctionnement quotidien (par exemple, fatigue, concentration, mémoire, humeur) ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

7. À quel point considérez-vous que vos difficultés de sommeil sont **REMARQUÉES** par les autres en termes de détérioration de votre qualité de vie ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

8. À quel point êtes-vous **INQUIET(E)/PRÉOCCUPÉ(E)** par vos difficultés actuelles de sommeil ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

9. Depuis combien de temps ressentez-vous des difficultés de sommeil ?
   En mois : (nombre)
   En années : (nombre)

10. Combien de nuits par semaine pensez-vous avoir des (nombre) difficultés de sommeil ?
    Par semaine (nombre)

11. Avez-vous de la difficulté à rester éveillé le jour ?

Aucunement	Légèrement	Moyennement	Beaucoup	Extrêmement
0	1	2	3	4

12. Avez-vous d'autres difficultés de sommeil ? Si oui, veuillez en préciser la nature :
    _____ cauchemars, _____ difficultés à respirer, _____ ronflement, _____ parler dans votre sommeil, _____ marcher dans votre sommeil, _____ mouvements des membres inférieurs.

13. À quel âge, vos difficultés de sommeil ont-elles débuté ? _____ ans
    Veuillez passer à la question n° 15.

14. **Histoire :**
    Avez-vous eu dans le passé des difficultés de sommeil ayant persisté pour plus d'un mois ?
    OUI NON
    Si non, veuillez passer à la question n° 15.
    Si oui, pour quelle durée ? _____ mois _____ années
    Quel âge aviez-vous à ce moment ? _____ ans
    Quelle était la nature de ces difficultés ? _____
    (voir question n° 12).

15. Souffrez-vous actuellement d'un trouble anxieux ou dépressif ?

16. Prenez-vous actuellement un traitement à visée psychologique ?

Score

Pour analyser et interpréter ce questionnaire, additionnez les notes données aux questions 4a, 4b, 4c, 5, 6, 7 et 8. Le score total s'établit entre 0 et 28.

0–7	Pas d'insomnie
8–14	Insomnie légère
15–21	Insomnie modérée
22–28	Insomnie sévère

Référence

Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001 ; 2 : 297–307.

Name: _____ **Date:** _____

1. Please rate the current (i.e., last 2 weeks) **SEVERITY** of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
Difficulty falling asleep:	0	1	2	3	4
Difficulty staying asleep:	0	1	2	3	4
Problem waking up too early:	0	1	2	3	4

2. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied				Very Dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

4. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	Barely	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

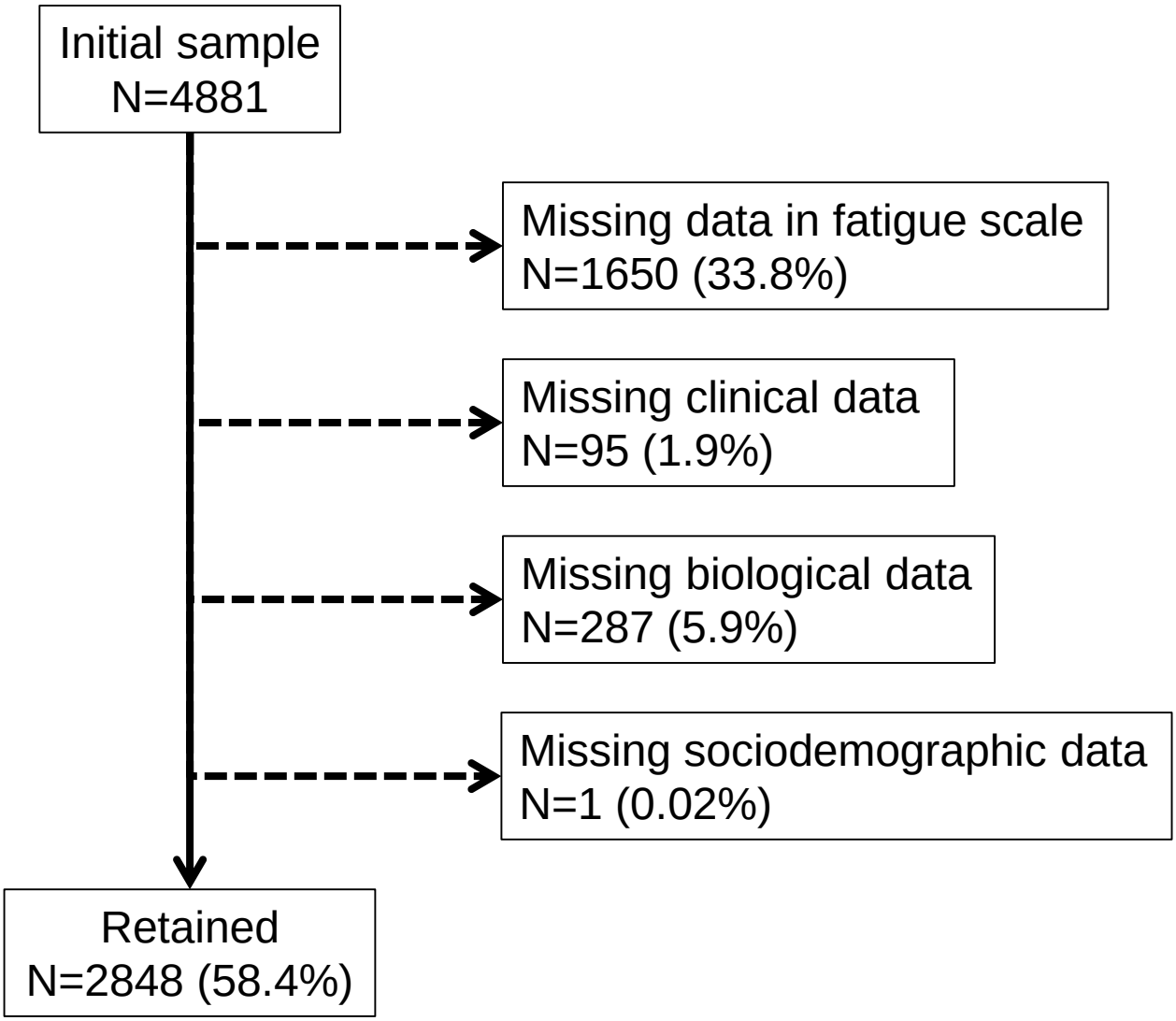
5. How **WORRIED**/distressed are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

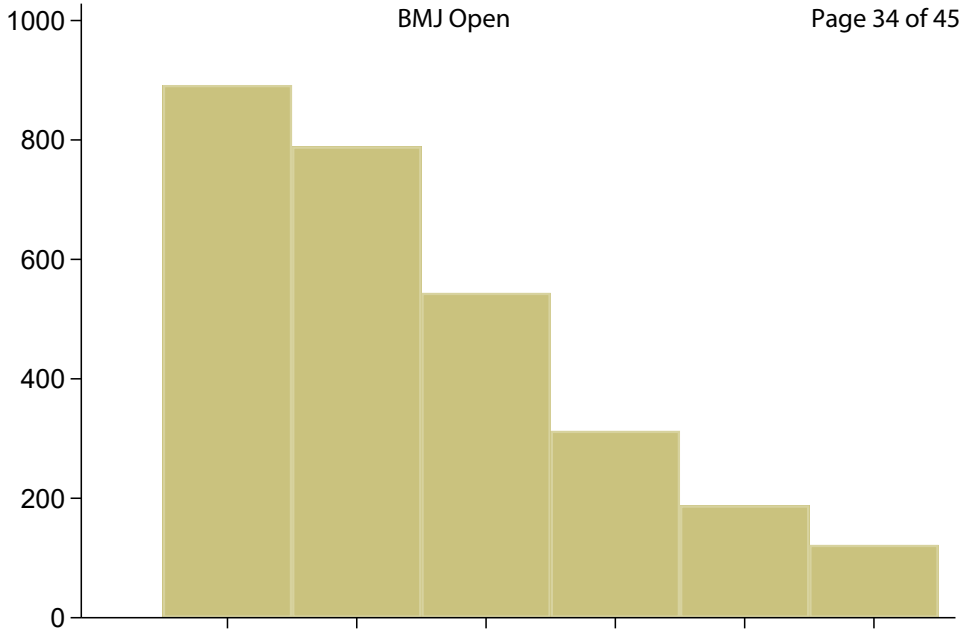
Guidelines for Scoring/Interpretation:

Add scores for all seven items (1a+1b+1c+ 2+3+4+5) = _____
Total score ranges from 0-28
0-7 = No clinically significant insomnia
8-14 = Subthreshold insomnia
15-21 = Clinical insomnia (moderate severity)
22-28 = Clinical insomnia (severe)

Supplemental figure 1: The reasons for exclusion



Exclusion if missing data in fatigue scale, missing clinical, biological and sociodemographic data



Supplemental table 1: comparison between excluded and included participants

	Included	Excluded	p-value
N	2848	2033	
Woman (%)	1514 (53.2)	1175 (57.8)	0.001
Age (years)	61.5 ± 9.8	65.0 ± 11.0	<0.001
Age groups			<0.001
45-54	879 (30.9)	467 (23.0)	
55-64	933 (32.8)	569 (28.0)	
64-74	739 (26.0)	560 (27.6)	
75+	297 (10.4)	437 (21.5)	
Educational level			<0.001
University	683 (24.0)	348 (17.2)	
High school	808 (28.4)	450 (22.2)	
Apprenticeship	1015 (35.6)	734 (36.2)	
Primary	342 (12.0)	497 (24.5)	
Smoking categories			0.015
Never	1149 (41.3)	737 (43.1)	
Former	1130 (40.6)	624 (36.5)	
Current	505 (18.1)	350 (20.5)	
BMI (kg/m^2)	26.4 ± 4.5	26.5 ± 5.0	0.525
BMI categories			0.038
Underweight	42 (1.5)	33 (2.0)	
Normal	1139 (40.0)	643 (39.4)	
Overweight	1157 (40.6)	618 (37.8)	
Obese	510 (17.9)	339 (20.8)	
Caffeinated drinks			<0.001
None	280 (10.1)	182 (11.3)	
1-3/day	1792 (64.7)	1108 (69.0)	
4-6/day	608 (21.9)	272 (16.9)	
7+/day	92 (3.3)	44 (2.7)	
Self-rated health			<0.001
Very good	679 (23.8)	353 (17.8)	
Good	1617 (56.8)	1094 (55.2)	
Average	502 (17.6)	464 (23.4)	
Bad + Very bad	50 (1.8)	72 (3.6)	
Cardiovascular disease	245 (8.6)	274 (13.5)	<0.001
Diabetes	226 (8.0)	256 (15.0)	<0.001
Depression	329 (11.9)	93 (11.9)	0.971
Anemia	109 (3.8)	108 (6.5)	<0.001
Ferritin [mcg/l]	227 [147 - 2.97]	220 [141 - 2.93]	0.058
TSH [mUI/l]	3.0 [2.1 - 3.0]	3.0 [2.1 - 2.9]	0.375
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 3.3	0.534
Anti-hypertensive drugs	885 (31.1)	812 (39.9)	<0.001
Anti-histaminics	68 (2.4)	32 (1.6)	0.048
Antidepressants	278 (9.8)	246 (12.1)	0.009
Hypnotics	122 (4.3)	145 (7.1)	<0.001

BMI, body mass index. Results are expressed as number of participants (column percentage) for categorical variables and as average±standard deviation or median [interquartile range] for continuous variables. Between-group comparison performed using chi-square for categorical variables and using student's t-test or Kruskal-Wallis test (§) for continuous variables.

Supplemental table 2: variables used to compute the propensity score

	Odds ratio (95% CI)	p-value
Gender (woman vs. man)	0.77 (0.64 - 0.93)	0.006
Age groups		
45-54	1 (ref)	
55-64	0.85 (0.68 - 1.07)	0.178
64-74	0.81 (0.63 - 1.03)	0.083
75+	0.50 (0.37 - 0.67)	<0.001
Educational level		
Primary	1 (ref)	
Apprenticeship	1.45 (1.11 - 1.91)	0.007
High school	1.58 (1.19 - 2.10)	0.002
University	1.51 (1.12 - 2.04)	0.007
Smoking categories		
Never	1 (ref)	
Former	1.15 (0.95 - 1.39)	0.155
Current	1.08 (0.85 - 1.39)	0.523
BMI categories		
Underweight	0.80 (0.43 - 1.49)	0.479
Normal	1 (ref)	
Overweight	1.39 (1.14 - 1.69)	0.001
Obese	1.57 (1.20 - 2.05)	0.001
Caffeinated drinks		
None		
1-3/day	1.14 (0.86 - 1.51)	0.369
4-6/day	1.29 (0.93 - 1.78)	0.129
7+/day	1.16 (0.66 - 2.03)	0.599
Self-rated health		
Very good	1 (ref)	
Good	0.98 (0.79 - 1.21)	0.836
Average	1.08 (0.80 - 1.45)	0.610
Bad + Very bad	1.22 (0.55 - 2.73)	0.621
Diabetes (yes vs. no)	0.69 (0.50 - 0.94)	0.021
Anemia (yes vs. no)	0.82 (0.54 - 1.26)	0.369

BMI, body mass index. Results are expressed as multivariable-adjusted odds ratio (95% confidence interval). Multivariable analysis performed using logistic regression.

Supplemental table 3: Bivariate and multivariable analysis of the continuous determinants of fatigue as defined by a Fatigue Severity Scale ≥5 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable		
	No fatigue	**Fatigue**	**p-value**	**No fatigue**	**Fatigue**	**p-value**
N	2538	310		2538	310	
Age (years)	61.7 ± 9.8	60.0 ± 10.0	0.005			
BMI (kg/m^2)	26.2 ± 4.4	27.8 ± 5.4	<0.001			
Handgrip (kg)	35.0 ± 12.0	32.8 ± 11.4	0.002	35.1 ± 0.1	35.4 ± 0.5	0.453
Ferritin [mcg/l]	149 [91 - 229]	138 [84 - 208]	0.083 §	185.1 ± 3.5	205.1 ± 11.3	0.098
TSH [mUI/l]	2.1 [1.5 - 3.0]	2.1 [1.5 - 3.0]	1.000 §	2.5 ± 0.1	2.5 ± 0.1	0.987
Free T4 [pmol/l]	16.2 ± 2.5	16.2 ± 2.6	0.968	16.3 ± 0.1	16.2 ± 0.2	0.881

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average ± standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average± standard error for the multivariable analysis. Bivariate analysis performed using student's t-test or Kruskal-Wallis nonparametric test (§). Multivariable analysis conducted using analysis of variance adjusting for gender, age group, BMI categories, insomnia categories, educational level, diabetes, presence of antihistaminic, antidepressive or hypnotic drugs, self-rated health and depression.

Supplemental table 4: Bivariate and multivariable analysis of the categorical determinants of fatigue as defined by a Fatigue Severity Scale ≥5 in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate			Multivariable model 1		Multivariable model 2	
	No fatigue	**Fatigue**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Gender			0.011				
Man	1210 (47.7)	124 (40.0)		1 (ref)		1 (ref)	
Woman	1328 (52.3)	186 (60.0)		1.45 (1.05 - 1.99)	0.024	1.43 (1.04 - 1.95)	0.027
Age group			<0.001				
45-54	758 (29.9)	121 (39)		1 (ref)		1 (ref)	
55-64	829 (32.7)	104 (33.6)		0.70 (0.49 – 1.00)	0.051	0.70 (0.49 - 0.99)	0.045
64-74	691 (27.2)	48 (15.5)		0.42 (0.27 - 0.64)	<0.001	0.41 (0.26 - 0.63)	<0.001
75+	260 (10.2)	37 (11.9)		0.81 (0.48 - 1.35)	0.416	0.79 (0.48 - 1.32)	0.370
Educational level			0.106				
Primary	293 (11.5)	49 (15.8)		1 (ref)			
Apprenticeship	905 (35.7)	110 (35.5)		1.03 (0.64 - 1.67)	0.902	-	
High school	720 (28.4)	88 (28.4)		1.11 (0.67 - 1.82)	0.687	-	
University	620 (24.4)	63 (20.3)		1.10 (0.65 - 1.86)	0.728	-	
Smoking categories			0.762				
Never	1028 (41.4)	121 (40.2)		-		-	
Former	1002 (40.4)	128 (42.5)		-		-	
Current	453 (18.2)	52 (17.3)		-		-	
BMI categories			<0.001				
Underweight	41 (1.6)	1 (0.3)		0.22 (0.03 - 1.85)	0.162	0.22 (0.03 - 1.85)	0.162
Normal	1032 (40.7)	107 (34.5)		1 (ref)		1 (ref)	
Overweight	1041 (41.0)	116 (37.4)		0.94 (0.66 - 1.34)	0.742	0.94 (0.66 - 1.33)	0.715
Obese	424 (16.7)	86 (27.7)		1.40 (0.93 - 2.08)	0.103	1.38 (0.93 - 2.06)	0.109
Insomnia categories			<0.001				
No insomnia	1972 (84.3)	145 (54.9)		1 (ref)		1 (ref)	
Subthreshold	288 (12.3)	59 (22.4)		1.45 (0.98 - 2.16)	0.064	1.46 (0.98 - 2.15)	0.060
Clinical insomnia	79 (3.4)	60 (22.7)		3.90 (2.41 - 6.33)	<0.001	3.82 (2.36 - 6.18)	<0.001
Caffeinated drinks			0.278				
None	240 (9.7)	40 (13.3)		-		-	

1-3/day	1603 (64.9)	189 (62.8)		-		-	
4-6/day	546 (22.1)	62 (20.6)		-		-	
7+/day	82 (3.3)	10 (3.3)		-		-	
Self-rated health			<0.001				
Very good	656 (25.9)	23 (7.4)		1 (ref)		1 (ref)	
Good	1505 (59.3)	112 (36.1)		1.61 (0.98 - 2.64)	0.062	1.58 (0.96 - 2.60)	0.069
Average	358 (14.1)	144 (46.5)		5.80 (3.40 - 9.87)	<0.001	5.65 (3.34 - 9.58)	<0.001
Bad + Very bad	19 (0.8)	31 (10.0)		17.7 (7.32 - 42.6)	<0.001	17.2 (7.16 - 41.1)	<0.001
Cardiovascular disease			0.617				
No	2322 (91.5)	281 (90.7)		-		-	
Yes	216 (8.5)	29 (9.4)		-		-	
Diabetes			0.006				
No	2343 (92.5)	273 (88.1)		1 (ref)		1 (ref)	
Yes	189 (7.5)	37 (11.9)		0.99 (0.58 - 1.70)	0.975	0.99 (0.58 - 1.69)	0.979
Depression (CES-D)			<0.001				
No	2260 (91.8)	170 (57.4)		1 (ref)		1 (ref)	
Yes	203 (8.2)	126 (42.6)		3.31 (2.28 - 4.79)	<0.001	3.34 (2.31 - 4.83)	<0.001
Anemia			0.325				
No	2444 (96.3)	295 (95.2)		1 (ref)		-	
Yes	94 (3.7)	15 (4.8)		1.24 (0.60 - 2.59)	0.557	-	
Ferritin categories			0.971				
>50	2294 (90.4)	280 (90.3)		-		-	
Normal + low	244 (9.6)	30 (9.7)		-		-	
TSH categories			0.842				
High > 4.22	223 (8.8)	30 (9.7)		1.50 (0.92 - 2.44)	0.105	-	
Normal 0.27-4.22	2294 (90.4)	277 (89.4)		1 (ref)		-	
Low < 0.27	21 (0.8)	3 (1.0)		0.63 (0.13 - 3.11)	0.566	-	
Free T4 categories			0.636				
High > 22	58 (2.3)	6 (1.9)		-		-	
Normal 12-22	2419 (95.3)	294 (94.8)		-		-	
Low < 12	61 (2.4)	10 (3.2)		-		-	
Anti-hypertensive			0.461				
No	1755 (69.2)	208 (67.1)		-		-	

Yes	783 (30.9)	102 (32.9)		-		-	
Anti-histaminics			0.156				
No	2481 (97.8)	299 (96.5)		1 (ref)		-	
Yes	57 (2.3)	11 (3.6)		1.06 (0.47 - 2.42)	0.882	-	
Antidepressants			<0.001				
No	2330 (91.8)	240 (77.4)		1 (ref)		1 (ref)	
Yes	208 (8.2)	70 (22.6)		1.48 (0.97 - 2.25)	0.070	1.46 (0.96 - 2.21)	0.076
Hypnotics			0.004				
No	2439 (96.1)	287 (92.6)		1 (ref)		1 (ref)	
Yes	99 (3.9)	23 (7.4)		0.61 (0.31 - 1.23)	0.167	0.63 (0.31 - 1.26)	0.190

BMI, body mass index; -, not retained. Results are expressed as number of participants (row percentage) for the bivariate analysis and as multivariable-adjusted odds ratio (95% confidence interval) for the multivariable analysis. Bivariate analysis performed using chi-square; multivariable analysis performed using logistic regression. Two multivariable models were applied: model 1 included all variables significantly ($p<0.05$) associated with fatigue using the threshold of ≥4 of the fatigue severity scale, while model 2 included only the variables significantly ($p<0.05$) associated with fatigue using the threshold of ≥5 of the fatigue severity scale.

Supplemental table 5: Multivariable analysis of the categorical determinants of fatigue (defined as a fatigue severity score ≥4) in the CoLaus study, Lausanne, Switzerland, 2014-2017, using inverse probability weighting.

	OR (95% CI)	P-value
Gender (woman vs. man)	1.26 (0.99 - 1.61)	0.064
Age group		
45-54	1 (ref)	
55-64	0.70 (0.53 - 0.91)	0.009
64-74	0.43 (0.31 - 0.59)	<0.001
75+	0.64 (0.42 - 0.96)	0.031
Educational level		
Primary	1 (ref)	
Apprenticeship	1.02 (0.70 - 1.48)	0.923
High school	1.08 (0.74 - 1.59)	0.678
University	0.94 (0.63 - 1.41)	0.768
BMI categories		
Underweight	0.71 (0.20 - 2.56)	0.598
Normal	1 (ref)	
Overweight	1.03 (0.79 - 1.34)	0.833
Obese	1.44 (1.05 - 1.98)	0.022
Insomnia categories		
No insomnia	1 (ref)	
Subthreshold	1.57 (1.15 - 2.14)	0.004
Clinical insomnia	3.74 (2.29 - 6.10)	<0.001
Self-rated health		
Very good	1 (ref)	
Good	1.92 (1.37 - 2.69)	<0.001
Average	5.51 (3.71 - 8.17)	<0.001
Bad + Very bad	17.2 (7.51 - 39.3)	<0.001
Diabetes (yes vs. no)	1.15 (0.76 - 1.74)	0.501
Depression (CES-D, yes vs. no)	3.21 (2.34 - 4.42)	<0.001
Anemia (yes vs. no)	1.58 (0.91 - 2.76)	0.107
TSH categories		
High > 4.22	1.15 (0.77 - 1.70)	0.499
Normal 0.27-4.22	1 (ref)	
Low < 0.27	3.30 (1.09 - 10.0)	0.035
Anti-histaminics (yes vs. no)	1.33 (0.69 - 2.57)	0.398
Antidepressants (yes vs. no)	1.39 (0.98 - 1.97)	0.069
Hypnotics (yes vs. no)	0.59 (0.31 - 1.10)	0.098

Results are expressed as multivariable-adjusted odds ratio (OR) and (95% confidence interval - CI). Multivariable analysis performed using logistic regression with inverse probability weighting.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Suppl figure 1
		(b) Give reasons for non-participation at each stage	Suppl figure 1
		(c) Consider use of a flow diagram	Suppl figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Suppl table 1

		(b) Indicate number of participants with missing data for each variable of interest	Suppl figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl table 2-3-4-5
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21