

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027070
Article Type:	Research
Date Submitted by the Author:	04-Oct-2018
Complete List of Authors:	Galland, Coralie; Centre Hospitalier Universitaire Vaudois, Médecine Marques-Vidal, Pedro-Manuel; Centre Hospitalier Universitaire Vaudois, Médecine Vollenweider, Peter; Lausanne University Hospital, Internal Medicine
Keywords:	fatigue, prevalence, fatigue severity scale, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

Peer review only

1  
2  
3 **Prevalence and determinants of fatigue in the Swiss population: A**  
4 **population based cross-sectional survey**  
5

6 Coralie Galland-Decker, Pedro Marques-Vidal and Peter Vollenweider  
7

8 Department of Medicine, Internal Medicine, Lausanne university hospital, Lausanne,  
9  
10 Switzerland  
11

12  
13 **Authors' emails:**

14 Coralie Galland-Decker: [Coralie.Galland@chuv.ch](mailto:Coralie.Galland@chuv.ch)

15 Pedro Marques-Vidal: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)

16  
17 Peter Vollenweider: [Peter.Vollenweider@chuv.ch](mailto:Peter.Vollenweider@chuv.ch)  
18  
19

20  
21 **Address for correspondence and reprints**

22 Pedro Marques-Vidal

23 Office BH10-642.

24 Department of Medicine, Internal Medicine.

25 Lausanne university hospital.

26 Rue du Bugnon 46, 1011, Lausanne, Switzerland.

27  
28 Phone: +41 21 314 09 34  
29

30 Email: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)  
31  
32

33  
34 **Word count:** 3153  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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  $\geq 4$  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”.<sup>1</sup> Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities.<sup>1</sup> Indeed, fatigue is a common symptom in the general population, with prevalence rates varying between 4 and 45%.<sup>2-4</sup> This ten-fold range in prevalence rates is likely due to the different methods used to assess fatigue.<sup>5</sup>

In healthy subjects, fatigue is a natural occurrence after physical or mental efforts, and is usually relieved by rest.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> Fatigue has also been associated with female sex,<sup>6,9</sup> older age<sup>10,11</sup> and lower socioeconomic status,<sup>10,11</sup> although the association with the last two determinants was not found in some studies.<sup>6,12</sup> Importantly, most studies on fatigue have been conducted in selected populations like workers<sup>13</sup> or general practice attendees.<sup>12,14,15</sup> To our knowledge, only two studies have assessed the prevalence of fatigue in the general population<sup>6,16</sup> and only a few have explored the determinants of fatigue in the general population.<sup>9-11,17-19</sup> 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.<sup>20</sup> 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).<sup>21</sup> This questionnaire has been validated for a general healthy population in the Swiss setting<sup>22</sup> and has a high test-retest reliability.<sup>5</sup> 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  $\geq 4$  is considered as having severe fatigue.<sup>21</sup>

### 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).<sup>23</sup> 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,

1  
2  
3 sleep dissatisfaction, interference of sleep disturbances with daytime functioning,  
4 noticeability of sleep problems by others, and distress caused by the sleep difficulties. Items  
5 were scaled 0-4 and then summed to obtain the global ISI score (range: 0-28). Clinically  
6 significant insomnia was defined as an ISI score  $\geq 15$  (moderate to severe intensity).<sup>23</sup>  
7  
8  
9

10  
11 Depression was assessed the CES-D <sup>24</sup> is a 20 items self-report instrument  
12 developed for research in the general population is used to assess the severity of depressive  
13 symptoms over the past week on a 4-point scale. It was translated into French by Fuhrer and  
14 Rouillon.<sup>25</sup> It has been used in other recent epidemiological studies assessing the link  
15 between depression and cardiovascular risk factors. The questionnaire is composed of 20  
16 questions; responses are graded using a Likert scale from 0 to 3, where 0 indicates rarely or  
17 none of the time (less than one day) and 4 most or all of the time (5-7 days per week). The  
18 final score is the sum of the 20 responses (possible range is 0-60), and a score  $\geq 16$  is  
19 considered as a risk for depression.  
20  
21  
22  
23  
24  
25  
26  
27  
28

29  
30 Self-rated health was assessed by a single question where participants had to rate  
31 their current health status from five categories ranging from “very bad” to “very good”. As the  
32 number of participants rating their health as “very bad” was very small, they were grouped  
33 with the participants who rated their health as “bad”.  
34  
35  
36  
37

38  
39 Body weight and height were measured with participants standing without shoes in  
40 light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a  
41 Seca™ scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using  
42 a Seca™ height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as  
43 weight/height<sup>2</sup> and categorized as underweight (BMI < 18.5 kg/m<sup>2</sup>), normal (18.5 ≤ BMI < 25  
44 kg/m<sup>2</sup>); overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>) and obese (BMI ≥ 30 kg/m<sup>2</sup>).  
45  
46  
47  
48  
49

50  
51 Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer  
52 (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders  
53 adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 between 0 and 30° of dorsiflexion. Three measurements were performed consecutively with  
4 the right hand and the highest value (expressed in kg) was included in the analyses.  
5  
6

7 Biological assays were performed by the CHUV Clinical Laboratory on fresh blood  
8 samples within 2 hours of blood collection, and additional aliquots were stored at –80°C. All  
9 measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland).  
10 The following analytical procedures (with maximum inter and intra-batch CVs) were used:  
11 high sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by  
12 immunoassay (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin  
13 was assessed by immunoturbidimetric method (Tina-quant 4<sup>th</sup> generation, Roche  
14 Diagnostics, Switzerland) with a maximum intra-assay CV of 7.2% and a maximum inter-  
15 assay CV of 9.9%. Thyroid stimulating hormone (TSH) and free T<sub>4</sub> were assessed by  
16 chemiluminescence (ECLIA) on a Cobas e602 device (Roche diagnostics GmbH,  
17 Mannheim, Germany) with intra-batch CVs ranging between 1.1% and 3.0% for TSH and  
18 between 2.7% and 5% for free T<sub>4</sub>.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

### 31 **Exclusion criteria**

32  
33 Participants were excluded if they lacked fatigue questionnaire, socioeconomic or  
34 clinical covariates and biological measures.  
35  
36  
37

### 38 **Ethical statement and consent**

39  
40 The institutional Ethics Committee of the University of Lausanne, which afterwards  
41 became the Ethics Commission of Canton Vaud ([www.cer-vd.ch](http://www.cer-vd.ch)) approved the baseline  
42 CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09)  
43 and the second (reference 26/14) follow-up. The full decisions of the CER-VD can be  
44 obtained from the authors upon request. The study was performed in agreement with the  
45 Helsinki declaration and its former amendments, and in accordance with the applicable  
46 Swiss legislation. All participants gave their signed informed consent before entering the  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60 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<sup>26</sup>. 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
<b>N</b>	2225	623				
Age (years)	61.9 ± 9.8	60.0 ± 9.8	<0.001	-	-	
BMI (kg/m <sup>2</sup> )	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		

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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**).

1  
2  
3 Multivariable analysis showed that obesity [odds-ratio (OR) and 95% confidence  
4 interval: 1.40 (1.03-1.91)], insomnia categories (p-value for trend <0.001), depression [3.26  
5 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend  
6 <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively  
7 associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-  
8 histaminics or hypnotics (**Table 2**).

9  
10  
11 Sensitivity analysis using inverse probability weighting led to similar findings, except that  
12 anaemia and antidepressants were no longer associated with fatigue, while a positive  
13 association was found between low TSH levels and fatigue (**Supplemental table 2**).

## 21 **DISCUSSION**

22  
23  
24 To our knowledge, this is one of the few studies assessing the prevalence and  
25 determinants of fatigue in a general population setting, and the first study conducted in  
26 Switzerland. Our results indicate that one out of five people aged between 45 and 86 years  
27 presents with fatigue, and that obesity, insomnia, depression and decreasing self-rated  
28 health status were positively associated, while older age was negatively associated with  
29 fatigue.

### 36 **Prevalence of fatigue**

37  
38 Fatigue was present in one out of five participants (22.1%), a finding in agreement  
39 with the sole two studies that assessed fatigue in the general population. The study by Loge  
40 et al. <sup>6</sup> reported a prevalence of 22% using the Chalder fatigue scale, while the study by  
41 Lerdal et al. <sup>16</sup> reported a prevalence of 23.1% using the FSS. Still, the study by Lerdal et al.  
42 used a higher cut-off ( $\geq 5$ ) to define fatigue, while we used the original threshold ( $\geq 4$ ).<sup>21 22</sup>  
43  
44 Using a cut-off  $\geq 4$ , the prevalence of fatigue in the study by Lerdal et al. was 46.7%, which  
45 was considered as an overestimation. A study conducted in general practice attendees  
46 reported a prevalence of fatigue 38% using the Chalder fatigue scale,<sup>15</sup> and a study  
47 conducted in the Danish working population reported a prevalence of fatigue of 22% using  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 other fatigue measures.<sup>13</sup> Overall, our results suggest that the prevalence of fatigue in the  
4 Lausanne population is comparable of even lower than reported previously.  
5  
6

### 7 **Clinical and societal determinants of fatigue**

8  
9 Women tended to report fatigue more frequently than men, but this association was  
10 no longer significant after multivariable adjustment. Higher prevalence of fatigue in women  
11 has been found in some studies<sup>6 9</sup> but not in others.<sup>12</sup> In a Swedish study conducted in  
12 2014, Engberg et al.<sup>10</sup> considered that this difference could be due factors related to gender  
13 inequalities regarding household responsibilities and child raising, as the gender gap in  
14 general fatigue was largest among those aged <55 years.  
15  
16  
17  
18  
19  
20

21 Younger people reported fatigue more frequently than elderly, a finding in agreement  
22 with a Swedish study conducted in 2014.<sup>10</sup> Similarly, in a previous study we found, that older  
23 subjects complain less of sleepiness.<sup>27</sup> Conversely, earlier studies (1990-2000) found a  
24 positive association between age and fatigue.<sup>6 11 19</sup> A possible explanation for this difference  
25 is that older people might have a better quality of life nowadays and are less depressed.  
26 Indeed, in our study, the lowest prevalence of fatigue was reported by participants aged 64-  
27 74 years, which are the “young” retired with few comorbidities. Similarly, the prevalence of  
28 depression was lower in elderly than in younger participants (8.1% and 10.2% in the 65-74  
29 and the 75+ years, respectively, vs. 15.1% and 12.5% in the 45-54 and 55-64 years,  
30 respectively, p-value<0.001).  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 Obese subjects had a higher prevalence of fatigue, a finding in agreement with  
43 studies conducted in the USA<sup>28</sup> and in the UK.<sup>17</sup> Obesity is a risk factor for sleep apnoea,  
44 which leads to increased daytime sleepiness. Still, the association persisted after adjusting  
45 for insomnia, a finding in agreement with a study that showed that obese subjects have  
46 excessive fatigue independently of sleep-disordered breathing.<sup>29</sup> Because it excluded too  
47 much subjects, we did not correlate obesity and sleep-disordered breathing in our study. A  
48 possible explanation could be the increase in proinflammatory cytokines in obese subjects,<sup>30</sup>  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 which would lead to higher fatigue,<sup>31</sup> but other factors such as decreased physical fitness  
4 should be further explored.  
5

6  
7 A positive association was found between self-reported clinical insomnia and fatigue,  
8 and this association was independent of obesity, depression and antidepressant medication.  
9  
10 Fatigue is a core symptom of insomnia<sup>32</sup> and a Norwegian study conducted in 2014 showed  
11 that reducing insomnia severity led to a concomitant reduction in fatigue.<sup>33</sup> Interestingly,  
12 many subjects with sleep complaints do not consult for this issue,<sup>34</sup> which might lead to an  
13 underestimation of its prevalence. Overall, our results suggest that insomnia is an important  
14 and underestimated factor of fatigue.  
15  
16  
17  
18  
19  
20

21 Both depression and antidepressant medication were independently and positively  
22 associated with fatigue. The association between depression and fatigue has been  
23 repeatedly reported,<sup>17 35-37</sup> and the same applies for antidepressant medication.<sup>2</sup> Our results  
24 confirm the known association between depression and fatigue, and suggest that  
25 antidepressant treatment might not systematically relieve fatigue among depressive subjects.  
26  
27  
28  
29  
30

31  
32 A strong association was found between poor self-rated health and fatigue, a finding  
33 also reported elsewhere.<sup>10 13</sup> Low self-rated health has been associated with increased  
34 levels of inflammatory markers such as interleukin 6 and CRP,<sup>38</sup> which in turn could trigger  
35 fatigue. Conversely, increased fatigue might lead to a lower rating of oneself health status.  
36  
37 Due to the cross-sectional setting of our study, it is not yet possible to ascertain causality,  
38 but the ongoing follow-up of the CoLaus participants will provide the answer in the next  
39  
40  
41  
42  
43  
44  
45  
46  
47

#### 48 **Biological determinants of fatigue**

49 Participants with anaemia had a higher likelihood of reporting fatigue. This finding is  
50 in agreement with the literature,<sup>39 40</sup> although no association between fatigue and low  
51 haemoglobin levels was found in an UK study.<sup>17</sup> A possible explanation is that in the UK  
52 study, anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds  
53 used in our study (<133 g/l for men and <117 g/l for women). This led to a small sample size  
54  
55  
56  
57  
58  
59  
60



(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.<sup>7</sup> 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.<sup>7</sup> Basu et al. found no association between TSH categories and fatigue<sup>17</sup> and Canaris et al<sup>41</sup> 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<sup>2</sup> 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.<sup>42</sup> 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<sup>43</sup> 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).<sup>2</sup> 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.<sup>44</sup>

## 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.

## **FUNDING**

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401). The funding sources had no involvement in the study design, data collection, analysis and interpretation, writing of the report, or decision to submit the article for publication.

## **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.

## **ACKNOWLEDGEMENTS**

Not applicable.

**REFERENCES**

1. Mota DD, Pimenta CA. Self-report instruments for fatigue assessment: a systematic review. *Res Theory Nurs Pract* 2006;20(1):49-78. [published Online First: 2006/03/21]
2. Guessous I, Favrat B, Cornuz J, et al. [Fatigue: review and systematic approach to potential causes]. *Rev Med Suisse* 2006;2(89):2725-31. [published Online First: 2007/02/16]
3. MacKean PR, Stewart M, Maddocks HL. Psychosocial diagnoses occurring after patients present with fatigue. *Can Fam Physician* 2016;62(8):e465-72. [published Online First: 2016/08/16]
4. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. *J Epidemiol Community Health* 1992;46(2):92-7. [published Online First: 1992/04/01]
5. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;56(2):157-70. doi: 10.1016/S0022-3999(03)00371-4 [published Online First: 2004/03/16]
6. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;45(1):53-65. [published Online First: 1998/08/28]
7. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006;174(6):765-7. doi: 10.1503/cmaj.1031153 [published Online First: 2006/03/15]
8. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. *Arch Intern Med* 1993;153(24):2759-65. [published Online First: 1993/12/27]
9. Fieo RA, Mortensen EL, Lund R, et al. Assessing fatigue in late-midlife: increased scrutiny of the Multiple Fatigue Inventory-20 for community-dwelling subjects. *Assessment* 2014;21(6):706-12. doi: 10.1177/1073191114541143 [published Online First: 2014/07/06]
10. Engberg I, Segerstedt J, Waller G, et al. Fatigue in the general population- associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014. *BMC Public Health* 2017;17(1):654. doi: 10.1186/s12889-017-4623-y [published Online First: 2017/08/16]
11. Watt T, Groenvold M, Bjorner JB, et al. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. *J Epidemiol Community Health* 2000;54(11):827-33. [published Online First: 2000/10/12]

12. David A, Pelosi A, McDonald E, et al. Tired, weak, or in need of rest: fatigue among general practice attenders. *BMJ* 1990;301(6762):1199-202. [published Online First: 1990/11/24]
13. Bultmann U, Kant I, Kasl SV, et al. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. *J Psychosom Res* 2002;52(6):445-52. [published Online First: 2002/06/19]
14. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. *Psychol Med* 1995;25(5):895-905. [published Online First: 1995/09/01]
15. Pawlikowska T, Chalder T, Hirsch SR, et al. Population based study of fatigue and psychological distress. *BMJ* 1994;308(6931):763-6. [published Online First: 1994/03/19]
16. Lerdal A, Wahl A, Rustoen T, et al. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J Public Health* 2005;33(2):123-30. doi: 10.1080/14034940410028406 [published Online First: 2005/04/13]
17. Basu N, Yang X, Luben RN, et al. Fatigue is associated with excess mortality in the general population: results from the EPIC-Norfolk study. *BMC Med* 2016;14(1):122. doi: 10.1186/s12916-016-0662-y [published Online First: 2016/08/21]
18. Boter H, Manty M, Hansen AM, et al. Self-reported fatigue and physical function in late mid-life. *J Rehabil Med* 2014;46(7):684-90. doi: 10.2340/16501977-1814 [published Online First: 2014/05/14]
19. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie* 2003;26(2):140-4. doi: 10.1159/000069834 [published Online First: 2003/05/29]
20. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008;8:6. doi: 10.1186/1471-2261-8-6 [published Online First: 2008/03/28]
21. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. [published Online First: 1989/10/01]
22. Valko PO, Bassetti CL, Bloch KE, et al. Validation of the fatigue severity scale in a Swiss cohort. *Sleep* 2008;31(11):1601-7. [published Online First: 2008/11/19]

- 1  
2  
3 23. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome  
4 measure for insomnia research. *Sleep Med* 2001;2(4):297-307. [published Online First:  
5 2001/07/05]  
6  
7  
8 24. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General  
9 Population. *Applied Psychological Measurement* 1977;1(3):385-401.  
10  
11 25. R. Fuhrer FR. The French version of the CES-D (Center for Epidemiologic Studies-Depression  
12 Scale). *European Psychiatry* 1989;4(3):163-66.  
13  
14  
15 26. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in  
16 observational studies. *Multivariate Behav Res* 2011;46(3):399-424. doi:  
17 10.1080/00273171.2011.568786 [published Online First: 2011/08/06]  
18  
19  
20 27. Luca G, Haba Rubio J, Andries D, et al. Age and gender variations of sleep in subjects without  
21 sleep disorders. *Ann Med* 2015;47(6):482-91. doi: 10.3109/07853890.2015.1074271  
22  
23 [published Online First: 2015/08/01]  
24  
25  
26 28. Resnick HE, Carter EA, Aloia M, et al. Cross-sectional relationship of reported fatigue to obesity,  
27 diet, and physical activity: results from the third national health and nutrition examination  
28 survey. *J Clin Sleep Med* 2006;2(2):163-9. [published Online First: 2007/06/15]  
29  
30  
31 29. Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population  
32 sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol*  
33 *Metab* 2005;90(8):4510-5. doi: 10.1210/jc.2005-0035 [published Online First: 2005/06/09]  
34  
35  
36 30. Marques-Vidal P, Bochud M, Bastardot F, et al. Association between inflammatory and obesity  
37 markers in a Swiss population-based sample (CoLaus Study). *Obes Facts* 2012;5(5):734-44.  
38 doi: 10.1159/000345045 [published Online First: 2012/10/31]  
39  
40  
41 31. Vgontzas AN, Bixler EO, Chrousos GP. Obesity-related sleepiness and fatigue: the role of the  
42 stress system and cytokines. *Ann N Y Acad Sci* 2006;1083:329-44. doi:  
43 10.1196/annals.1367.023 [published Online First: 2006/12/07]  
44  
45  
46 32. Medicine AAs. The international classification of sleep disorders: diagnostic and coding  
47 manual2005:297pp.  
48  
49  
50 33. Kallestad H, Jacobsen HB, Landro NI, et al. The role of insomnia in the treatment of chronic  
51 fatigue. *J Psychosom Res* 2015;78(5):427-32. doi: 10.1016/j.jpsychores.2014.11.022  
52  
53 [published Online First: 2014/12/17]  
54  
55  
56  
57  
58  
59  
60

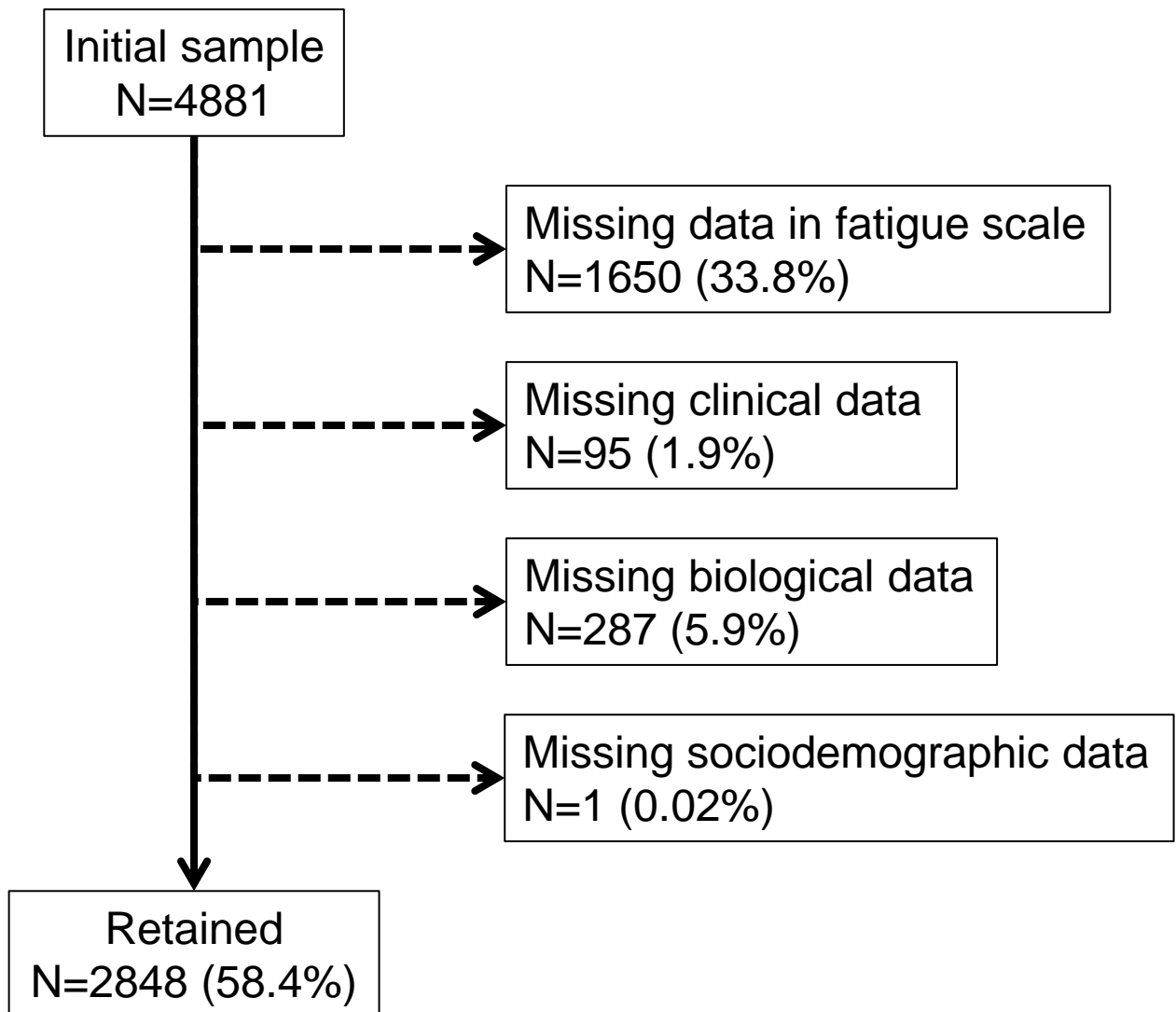
- 1  
2  
3 34. Pires ML, Benedito-Silva AA, Mello MT, et al. Sleep habits and complaints of adults in the city of  
4 Sao Paulo, Brazil, in 1987 and 1995. *Braz J Med Biol Res* 2007;40(11):1505-15. [published  
5 Online First: 2007/10/16]  
6  
7  
8 35. Lawrie SM, Manders DN, Geddes JR, et al. A population-based incidence study of chronic fatigue.  
9  
10 *Psychol Med* 1997;27(2):343-53. [published Online First: 1997/03/01]  
11  
12 36. Wessely S, Chalder T, Hirsch S, et al. Psychological symptoms, somatic symptoms, and  
13 psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in  
14 the primary care setting. *Am J Psychiatry* 1996;153(8):1050-9. doi: 10.1176/ajp.153.8.1050  
15 [published Online First: 1996/08/01]  
16  
17  
18 37. Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic fatigue  
19 and psychiatric morbidity: results from a community survey in Great Britain. *Int Rev Psychiatry*  
20 2003;15(1-2):57-64. doi: 10.1080/0954026021000045958 [published Online First: 2003/05/15]  
21  
22  
23 38. Christian LM, Glaser R, Porter K, et al. Poorer self-rated health is associated with elevated  
24 inflammatory markers among older adults. *Psychoneuroendocrinology* 2011;36(10):1495-504.  
25 doi: 10.1016/j.psyneuen.2011.04.003 [published Online First: 2011/05/24]  
26  
27  
28 39. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive  
29 minimal clinically important differences on the Functional Assessment of Cancer Therapy  
30 (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;24(6):547-61. [published  
31 Online First: 2003/01/29]  
32  
33  
34 40. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general  
35 United States population. *Cancer* 2002;94(2):528-38. doi: 10.1002/cncr.10245 [published  
36 Online First: 2002/03/20]  
37  
38  
39 41. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. *Arch*  
40 *Intern Med* 2000;160(4):526-34. [published Online First: 2000/03/01]  
41  
42  
43 42. Sleep complaints: Whenever possible, avoid the use of sleeping pills. *Prescrire Int*  
44 2008;17(97):206-12. [published Online First: 2009/06/20]  
45  
46  
47 43. Hasson D, Anderberg UM, Theorell T, et al. Psychophysiological effects of a web-based stress  
48 management system: a prospective, randomized controlled intervention study of IT and media  
49 workers [ISRCTN54254861]. *BMC Public Health* 2005;5:78. doi: 10.1186/1471-2458-5-78  
50 [published Online First: 2005/07/27]  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 44. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors  
4 relating to fatigue in men and women. *Med Care* 1999;37(10):1078-83. [published Online  
5 First: 1999/10/19]  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



## 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 <sup>2</sup> )	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
<b>Title and abstract</b>	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
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
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
<b>Results</b>		
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

<b>Discussion</b>		
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
<b>Other information</b>		
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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027070.R1
Article Type:	Research
Date Submitted by the Author:	05-Apr-2019
Complete List of Authors:	Galland, Coralie; Centre Hospitalier Universitaire Vaudois, Médecine Marques-Vidal, Pedro; Lausanne University Hospital, Department of Internal Medicine Vollenweider, Peter; Lausanne University Hospital, Internal Medicine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	General practice / Family practice
Keywords:	fatigue, prevalence, fatigue severity scale, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3 **Prevalence and factors associated with fatigue in the Lausanne**  
4 **middle-aged population: A population based cross-sectional**  
5 **survey**  
6

7 Coralie Galland-Decker, Pedro Marques-Vidal and Peter Vollenweider  
8  
9

10 Department of Medicine, Internal Medicine, Lausanne university hospital, Lausanne,  
11  
12 Switzerland  
13  
14

15 **Authors' emails:**

16 Coralie Galland-Decker: [Coralie.Galland@chuv.ch](mailto:Coralie.Galland@chuv.ch)

17 Pedro Marques-Vidal: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)

18 Peter Vollenweider: [Peter.Vollenweider@chuv.ch](mailto:Peter.Vollenweider@chuv.ch)  
19  
20  
21  
22

23 **Address for correspondence and reprints**

24 Pedro Marques-Vidal

25 Office BH10-642.

26 Department of Medicine, Internal Medicine.

27 Lausanne university hospital.

28 Rue du Bugnon 46, 1011, Lausanne, Switzerland.

29 Phone: +41 21 314 09 34

30 Email: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)  
31  
32  
33  
34  
35  
36  
37

38 **Word count:** 4513  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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  $\geq 4$  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.



1  
2  
3 **Keywords:** fatigue; prevalence; epidemiology; Fatigue severity scale  
4  
5

6 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
7

- 8 - This study assessed the prevalence and factors associated with fatigue in a general  
9 population setting.  
10  
11 - A large panel of associated with fatigue was evaluated.  
12  
13 - A list of the most frequent determinants was established, facilitating etiological  
14 search in clinical practice  
15  
16 - The study was limited to subjects aged 45 to 86, so results do not apply to younger  
17 or older groups.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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”.<sup>1</sup>

Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities.

<sup>1</sup> Indeed, fatigue is a common symptom with prevalence rates varying between 4 and 45%.<sup>2-</sup>

<sup>4</sup> This ten-fold range in prevalence rates is likely due to the different settings (i.e. general practice<sup>5</sup> or workers<sup>6</sup>) or the different methods used to assess fatigue.<sup>7</sup>

In healthy subjects, tiredness or sleepiness are a natural occurrence after physical or mental efforts, and are usually relieved by rest.<sup>8-9</sup> While fatigue is defined as extreme and persistent tiredness, weakness or exhaustion, of mental and/or physical origin<sup>7</sup> that is not relieved by rest. Fatigue is defined in duration as recent (<1 month) prolonged (1 to 6 months) and chronic (>6 months)<sup>10</sup>. 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)<sup>11</sup> or as idiopathic (absence of other symptoms).

Fatigue is one of the most common complaints reported in primary care<sup>12</sup> and is associated with a decreased quality of life and increased morbidity and mortality in the general population.<sup>13</sup> 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.<sup>10</sup> 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.<sup>14</sup> Fatigue has also been associated with female sex,<sup>8-15</sup> older age<sup>16-17</sup> and lower socioeconomic status,<sup>16-17</sup> although the association with the last two determinants were not found in some studies.<sup>8-18</sup> Importantly, most studies on fatigue have been conducted in selected populations such as workers<sup>6</sup> or general practice attendees.<sup>2-5-18</sup> To our knowledge, only two studies have assessed the prevalence of fatigue in the general population<sup>8-19</sup> and only a few have explored the

1  
2  
3 determinants of fatigue in the general population.<sup>13 15-17 20 21</sup> Furthermore, most studies focused  
4 on socio-economic and disease determinants of fatigue, while information regarding the  
5 biological determinants (i.e. anemia or thyroid pathology)<sup>13</sup> or the medications associated with  
6 fatigue is scarce. Moreover, to date, little is known about the prevalence of fatigue and its  
7 determinants in Switzerland.  
8  
9  
10  
11  
12

13  
14 Hence, this study aimed to examine the prevalence and the factors associated with  
15 fatigue in a population-based sample from the city of Lausanne, Switzerland.  
16  
17

## 18 19 **POPULATION AND METHODS**

### 20 21 **Study population**

22  
23 The CoLaus study is a population-based cohort exploring biological, genetic, and  
24 environmental determinants of cardiovascular diseases. Detailed descriptions of the study  
25 design have been reported elsewhere.<sup>22</sup> Briefly, a non-stratified random representative  
26 sample of the population of Lausanne was recruited between 2003 and 2006 using the  
27 following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate.  
28 The first follow-up was performed between April 2009 and September 2012 and the second  
29 follow-up between May 2014 and April 2017. At both baseline and subsequent follow-ups,  
30 participants were invited to attend a clinical examination at the Lausanne university hospital.  
31 Participants received a paper questionnaire at home, which they filled prior to the clinical  
32 examination. During the clinical examination, a second questionnaire regarding personal and  
33 family history of cardiovascular disease and cardiovascular risk factors was applied. For more  
34 details, please consult [www.colaus-psycolaus.ch](http://www.colaus-psycolaus.ch).  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49 As fatigue was only assessed in the second follow-up, data from the second follow-up,  
50 which included 4881 of the initial 6773 participants recruited at baseline, was used. At the  
51 second follow-up, participants were aged 45-86 years.  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Fatigue scale

Fatigue severity during the previous week was assessed by the 9 items Fatigue Severity Scale (FSS).<sup>9</sup> The FSS is one of the most commonly used fatigue questionnaires. It had been validated in a healthy population setting in German-speaking Switzerland<sup>23</sup>, Portugal<sup>24</sup> and Norway<sup>19</sup>. It is a simple, time-saving, self-administrated questionnaire allowing its use in large epidemiological studies and has a high test-retest reliability.<sup>7</sup> 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  $\geq 4$  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.<sup>9</sup> 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).<sup>25</sup> 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  $\geq 15$  (moderate to severe intensity).<sup>25</sup>

1  
2  
3 Depression was assessed with the CES-D <sup>26</sup>, a 20 item self-report instrument,  
4 developed for research in the general population, that is used to assess the severity of  
5 depressive symptoms over the past week on a 4-point scale. It was translated into French by  
6 Fuhrer and Rouillon.<sup>27</sup> It has been used in other recent epidemiological studies assessing the  
7 link between depression and cardiovascular risk factors <sup>28</sup>. The questionnaire is composed of  
8 20 questions; responses are graded from 0 to 3, where 0 indicates rarely or never (less than  
9 one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the  
10 20 responses (possible range is 0-60), and a score  $\geq 16$  is considered as a risk for depression.  
11  
12  
13  
14  
15  
16  
17  
18  
19

20 Self-rated health was assessed by a single question where participants had to rate  
21 their current health status from five categories ranging from “very bad” to “very good”. As the  
22 number of participants rating their health as “very bad” was very small, they were grouped with  
23 the participants who rated their health as “bad”.  
24  
25  
26  
27  
28

29 Body weight and height were measured with participants standing without shoes in  
30 light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™  
31 scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™  
32 height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as  
33 weight/height<sup>2</sup> and categorized as underweight (BMI < 18.5 kg/m<sup>2</sup>), normal (18.5 ≤ BMI < 25  
34 kg/m<sup>2</sup>); overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>) and obese (BMI ≥ 30 kg/m<sup>2</sup>).  
35  
36  
37  
38  
39  
40  
41  
42

43 Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer  
44 (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted  
45 and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and  
46 30° of dorsiflexion. Three measurements were performed consecutively with the right hand  
47 and the highest value (expressed in kg) was included in the analyses.  
48  
49  
50  
51  
52

53 Caffeinated drink consumption was assessed by the question “How many cups or cans  
54 of drinks containing caffeine (coffee, tea, coke or similar) do you drink per day?” with possible  
55 answers “None”, “1-3”, “4-6” and “7 or more”.  
56  
57  
58  
59  
60

1  
2  
3 Participants were asked to report all medications (prescribed or bought over the  
4 counter) they took during the last 6 months. Medications were coded using the Anatomical,  
5 Therapeutic Chemical (ATC) classification of the world health organization  
6 ([www.whooc.no/atc\\_ddd\\_index/](http://www.whooc.no/atc_ddd_index/)). Antihistamincs were defined as any ATC code beginning with  
7 "R06"; antidepressants were defined as an ATC code beginning with "N05BD" or "N06AA" or  
8 "N06AB" or "N06AF" or "N06AG" or "N06AX" or "N06CA"; hypnotics were defined as any ATC  
9 code beginning with "N05C". Antihypertensive drugs were defined by asking the participants  
10 if they were taking drugs for hypertension.  
11  
12  
13  
14  
15  
16  
17  
18  
19

20 Diabetes was defined by a fasting plasma glucose  $\geq 7$  mmol/L and/or the presence of  
21 an antidiabetic drug treatment (oral or insulin). Personal history of cardio vascular disease was  
22 assessed by asking the participant if he/she had sustained a coronary event (myocardial  
23 infarction or angina pectoris) or a stroke.  
24  
25  
26  
27  
28

29 Biological assays were performed by the CHUV Clinical Laboratory on fresh blood  
30 samples within 2 hours of blood collection, and additional aliquots were stored at  $-80^{\circ}\text{C}$ . All  
31 measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland).  
32 The following analytical procedures (with maximum inter and intra-batch CVs) were used: high  
33 sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay  
34 (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by  
35 immunoturbidimetric method (Tina-quant 4<sup>th</sup> generation, Roche Diagnostics, Switzerland) with  
36 a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid  
37 stimulating hormone (TSH) and free  $T_4$  were assessed by chemiluminescence (ECLIA) on a  
38 Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs  
39 ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free  $T_4$ .  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52

### 53 Exclusion criteria

54  
55 Participants were excluded if they lacked 1) any answer to the fatigue questionnaire;  
56  
57 2) clinical data such as age, body mass index, smoking, depression, insomnia or medications;  
58  
59  
60

1  
2  
3 3) biological measures such as haemoglobin or thyroid hormones and 4) socioeconomic data  
4 such as educational level.  
5  
6

### 7 **Ethical statement and consent**

8  
9  
10 The institutional Ethics Committee of the University of Lausanne, which afterwards  
11 became the Ethics Commission of Canton Vaud ([www.cer-vd.ch](http://www.cer-vd.ch)) approved the baseline  
12 CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and  
13 the second (reference 26/14) follow-up. The full decisions of the CER-VD can be obtained  
14 from the authors upon request. The study was performed in agreement with the Helsinki  
15 declaration and its former amendments, and in accordance with the applicable Swiss  
16 legislation. All participants gave their signed informed consent before entering the study.  
17  
18  
19  
20  
21  
22  
23

### 24 **Patient and Public Involvement**

25  
26  
27 No patients or public were involved in this study design, conduct or analysis.  
28  
29

### 30 **Statistical analysis**

31  
32 Statistical analysis was performed using Stata version 15.1 for windows (Stata Corp,  
33 College Station, Texas, USA). Prevalence rates for fatigue were expressed as percentage and  
34 95% confidence interval (CI). Descriptive results were expressed as number of participants  
35 (percentage) for categorical variables or as average $\pm$ standard deviation for continuous  
36 variables. Bivariate analyses were performed using chi-square or Fisher's exact test for  
37 categorical variables and student's t-test or Kruskal-Wallis test for continuous variables. All  
38 categorical variables significantly ( $p < 0.05$ ) associated with fatigue in the bivariate analysis  
39 were included in the multivariable analysis. Multivariable analysis was performed using  
40 analysis of variance or logistic regression with fatigue (dichotomized into yes/no) as dependent  
41 variable; results were expressed as multivariable-adjusted mean $\pm$ standard error for  
42 continuous variables or as Odds ratio (OR) and 95% CI for categorical variables.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54  
55  
56 Sensitivity analyses were conducted using a FSS threshold of 5. Further, as the  
57 number of excluded participants was high, other sensitivity analyses were conducted by  
58 creating a propensity score for being excluded<sup>29</sup>. The propensity score was computed using  
59  
60

1  
2  
3 logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly  
4 associated with exclusion as independent variables. A probability of exclusion was computed  
5 for each participant, and the inverse of the probability was used for weighting.  
6  
7  
8

9  
10 Statistical significance was assessed for a two-sided test with  $p < 0.05$ .  
11

## 12 **RESULTS**

### 13 **Study population**

14  
15  
16 Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for  
17 analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most  
18 frequent reason was lack of data regarding fatigue. The comparison between included and  
19 excluded participants is provided in **supplemental table 1** and the results of the multivariable  
20 analysis are provided in **supplemental table 2**. Excluded participants were more frequently  
21 women, were older, had a lower educational level, were more frequently never or current  
22 smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and  
23 hypertension) and rated their health worse.  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

### 40 **Prevalence and factors associated with fatigue**

41 The overall prevalence of fatigue as defined by a FSS  $\geq 4$  was 21.9% (95% CI: 20.4%  
42 – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% -  
43 22.3%),  $p = 0.031$ . The distribution of the FSS  $\geq 5$  (prevalence of fatigue 10.9%) is provided in  
44 **supplemental figure 2**; the number of participants with fatigue decreased when the levels of  
45 FSS increased.  
46  
47  
48  
49

50 The analysis of the factors associated with fatigue as defined by a FSS  $\geq 4$  is provided  
51 in **Tables 1 and 2**.  
52

53  
54  
55 **Table 1:** Bivariate and multivariable analysis of the continuous factors associated with  
56 fatigue as defined by a Fatigue Severity Scale  $\geq 4$  in the CoLaus study, Lausanne,  
57 Switzerland, 2014-2017.  
58  
59  
60



	Bivariate			Multivariable		
	No fatigue	Fatigue	p-value	No fatigue	Fatigue	p-value
<b>N</b>	2225	623				
Age (years)	61.9 ± 9.8	60.0 ± 9.8	<0.001	-	-	
BMI (kg/m <sup>2</sup> )	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  $\geq 4$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate		p-value	Multivariable	
	No fatigue	Fatigue		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)	

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

1  
2  
3 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend  
4 <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively  
5 associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-  
6 histaminics or hypnotics (**Table 2**).

### 11 **Sensitivity analyses**

12  
13  
14 The overall prevalence of fatigue as defined by a FSS  $\geq 5$  was 10.9% (95% CI: 9.7% –  
15 12.1%) and was higher in women 12.3% (10.7% - 14.0%) than in men 9.3% (7.8% - 11.1%),  
16 p=0.011. The results of the sensitivity analyses using a FSS threshold of  $\geq 5$  are provided in  
17 **supplemental tables 3 and 4**. Overall, the results were comparable with those using a  
18 threshold of  $\geq 4$ : gender, insomnia categories (p-value for trend <0.001), and low self-rated  
19 health status (p-value for trend <0.001) were positively associated with fatigue. Conversely,  
20 no association was found for age, obesity, diabetes, TSH levels, antihistaminics,  
21 antidepressives or hypnotics (**supplemental table 4**).

22  
23  
24 Sensitivity analysis using inverse probability weighting by the propensity score led to  
25 similar findings, except that anemia and antidepressants were no longer associated with  
26 fatigue, while a positive association was found between low TSH levels and fatigue  
27 (**Supplemental table 5**).

### 31 **DISCUSSION**

32  
33  
34 To our knowledge, this is one of the few studies assessing the prevalence and the  
35 factors associated with fatigue in a general population setting, and the first study conducted  
36 in Switzerland. Using a FSS cut-off  $\geq 4$ , our results indicate that one out of five people aged  
37 between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and  
38 decreasing self-rated health status were positively associated with fatigue; while older age  
39 was negatively associated with fatigue.

### Prevalence of fatigue

Using the cut-off of  $\geq 4$ , fatigue was present in one out of five participants (22.1%), a finding in agreement with the study by Loge et al.<sup>8</sup>, which reported a prevalence of 22% among 2323 participants using the Chalder fatigue scale. Conversely, the cross-sectional study by Lerdal et al.<sup>19</sup>, 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  $\geq 4$  and  $\geq 5$  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,<sup>2</sup> whereas a study conducted in the Dutch working population reported a prevalence of fatigue of 22% using other fatigue measures.<sup>6</sup> 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<sup>8 15</sup> but not in others.<sup>18</sup> In a Swedish study conducted in 2014, Engberg et al.<sup>16</sup> 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.<sup>16</sup> Similarly, a previous study found that older subjects complain less of sleepiness.<sup>30</sup> Still, this association was no longer statistically significant when the cut off of  $\geq 5$  was applied to define fatigue, suggesting that young subjects tend to present with borderline fatigue as suggested previously<sup>19</sup>. Conversely, earlier studies (1990-2000) found a positive association between age and fatigue.<sup>8 17 21</sup> 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

1  
2  
3 among Swiss elderly, the VLV study<sup>31</sup> concluded that quality of life among Swiss elderly  
4 increased in the last 30 years<sup>32</sup>. Indeed, in our study, the lowest prevalence of fatigue was  
5 reported by participants aged 64-74 years, which are the “young” retired with few  
6 comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger  
7 participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and  
8 12.5% in the 45-54 and 55-64 years, respectively, p-value<0.001).

9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Obese subjects had a higher prevalence of fatigue defined by a FSS  $\geq 4$ . This finding  
is in agreement with studies conducted in the USA<sup>33</sup> and in the UK.<sup>13</sup> . Still, this association  
was no longer statistically significant when the cut off of  $\geq 5$  was applied to define fatigue,  
suggesting that obese subjects tend to present with borderline fatigue as suggested previously  
<sup>19</sup>. 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.<sup>34</sup> 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,<sup>35</sup> which would lead to higher fatigue,<sup>36</sup> 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<sup>34</sup> and a Norwegian study conducted in 2014 showed  
that reducing insomnia severity led to a concomitant reduction in fatigue.<sup>37</sup> Interestingly, many  
subjects with sleep complaints do not consult for this issue,<sup>38</sup> 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,<sup>13 39-41</sup> and the same applies for antidepressant medication.<sup>3</sup> Our

1  
2  
3 results confirm the known association between depression and fatigue, and suggest that  
4 antidepressant treatment might not systematically relieve fatigue among depressive  
5 subjects. Furthermore, fatigue is a common side effect of antidepressant therapy and a  
6 symptom of depression, making the identification of the cause of fatigue difficult with a  
7 possibility of reverse causality (fatigue leading to depression and vice versa). We used a  
8 one-dimensional tool to evaluate fatigue (FSS); hence, we cannot distinguish between  
9 physical and mental fatigue. There is considerable overlap in phenomenology of fatigue  
10 and depression or anxiety but there are some important differences. People with fatigue  
11 without psychiatric symptoms tend to attribute their symptoms to external causes.  
12 Conversely, most depressed people experience self-blame or lowered self-esteem <sup>42</sup>.  
13 Further, fatigue and depression commonly appear together. A study conducted in 2009 by  
14 Harvey et al. <sup>43</sup>, showed that 7% of fatigued persons have no psychiatric symptoms, but  
15 remained at increased risk of later psychiatric disorder independently of the severity of  
16 fatigue.

17  
18 A strong association was found between poor self-rated health and fatigue, a finding  
19 also reported elsewhere.<sup>6 16</sup> Low self-rated health has been associated with increased levels  
20 of inflammatory markers such as interleukin 6 and CRP,<sup>44</sup> which in turn could trigger fatigue.  
21 Conversely, increased fatigue might lead to a lower rating of health status.

### 22 **Biological factors associated with fatigue**

23  
24 Participants with anemia had a higher likelihood of reporting fatigue. This finding is in  
25 agreement with the literature,<sup>45 46</sup> although no association between fatigue and low  
26 haemoglobin levels was found in a UK study. <sup>13</sup> A possible explanation is that in the UK study,  
27 anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds used in our  
28 study (<133 g/l for men and <117 g/l for women). This led to a small sample size (356  
29 participants, corresponding to 1.9% of the overall sample) and thus a low statistical power.

30  
31 Hypothyroidism is often cited during the investigation of fatigue.<sup>10</sup> In this study  
32 participants with low TSH levels reported fatigue more frequently, but this association was

1  
2  
3 significant only after multivariable analysis with inverse probability weighting. Furthermore, the  
4 prevalence of low TSH levels was <1% in the overall sample. The associations between  
5 hypothyroidism and fatigue have been controversial for a long time.<sup>10</sup> Basu et al. found no  
6 association between TSH categories and fatigue<sup>13</sup> and Canaris et al<sup>47</sup> reported that the  
7 association between fatigue and hypothyroidism was weak. Overall, our results suggest that,  
8 in presence of fatigue, hypothyroidism is an unlikely cause and should not be systematically  
9 assessed.  
10  
11  
12  
13  
14  
15  
16

### 17 18 **Implications of the study**

19  
20 Based on our study findings, we propose to focus on specific clinical and biological  
21 factors amenable to treatment at an individual level. Regarding clinical factors, sleep  
22 disturbances such as insomnia and sleep apnea (namely in presence of a patient with obesity)  
23 and the presence of depression should be assessed. Hence, lifestyle measures to improve  
24 sleep quality and quantity should be preferred to medication.<sup>22</sup> In the case of depression, it  
25 will be important to warn patients that antidepressor medication might not necessarily lead into  
26 rapid relief of fatigue. Regarding biological factors, anemia should be ruled out, while  
27 screening for hypothyroidism is not recommended as a first step.  
28  
29  
30  
31  
32  
33  
34  
35  
36

37 At the population level, preventive measures such as stress management and health  
38 promotion like relaxation, time management and cognitive reframing (for example within the  
39 work environment) could improve sleep quality, increase self-rated health {Hasson, 2005  
40 #615} and consequently reduce fatigue.  
41  
42  
43  
44  
45  
46  
47  
48

### 49 **Recommendations for future studies**

50 Future studies on the prevalence of fatigue in the general population should focus on  
51 the following topics: 1) validate the questionnaires in the population of interest; 2) whenever  
52 possible, use a standardised questionnaire to allow comparison between studies.  
53  
54  
55

56 While some factors such as obesity<sup>13 33</sup>, depression<sup>13 39-41</sup> and antidepressor  
57 medications<sup>3</sup> were consistently associated with fatigue in our study and in the literature,  
58  
59  
60



1  
2  
3 controversial findings such as the association between fatigue and gender, age groups and  
4  
5 anemia should be further explored.  
6  
7

### 8 **Strengths and limitations**

9  
10 This study has several strengths. Firstly, it is one of the few studies assessing the  
11 prevalence and the factors associated with fatigue in a population-based sample, which is of  
12 interest for public health. Secondly, it explored a large panel of possible factors associated  
13 with fatigue, thus allowing the identification of factors significantly and independently  
14 associated with fatigue.  
15  
16  
17  
18  
19

20  
21 This study has also several limitations. Firstly, its cross sectional setting precludes the  
22 identification of the causes of fatigue, as reverse causality is possible (i.e. fatigue leading to  
23 depression and vice-versa).<sup>3</sup> All participants of the CoLaus study are currently being re-  
24 contacted and re-examined, so a prospective analysis of the causes of fatigue will be feasible  
25 within two years. Secondly, there is no gold standard for the evaluation of fatigue and no  
26 official definition of fatigue. Hence, results might vary according to the scale applied or how  
27 participants interpret the term "fatigue". In this study, we chose to use a scale that was  
28 previously applied by other authors to facilitate comparisons. Thirdly, only the German version  
29 of the FSS has been validated in Switzerland; the French version used in this study has not  
30 yet been validated. Hence, it is possible that the true prevalence levels of fatigue might be  
31 under- or over-estimated, or that some items of the questionnaire might not be informative.  
32  
33 Still, the Cronbach's alpha for the questionnaire was 0.918, suggesting an excellent internal  
34 consistency. Furthermore, our results provide a first estimation of the prevalence of fatigue in  
35 the Swiss French-speaking general population, which could serve as a reference for further  
36 studies. Fourthly a sizable fraction of the sample was excluded, both between the baseline  
37 and the second follow-up, and within the current study, which might limit the generalizability  
38 of the findings. For instance, excluded participants were more frequently women; as women  
39 reported more frequently fatigue, this might lead to an underestimation of prevalence rates or  
40 a decrease in the strength of the associations. Still, an analysis using a propensity score  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 weighting for the probability of being excluded led to similar findings. Conversely, it was not  
4 possible to assess the reasons why participants did not complete the questionnaire. Fifthly,  
5 no information was available regarding shift work or the presence of very young children. Still,  
6 as a sizable fraction (almost 70%) of the sample was aged over 55 and over 36% of the sample  
7 was aged over 64, it is likely that the number of participants either on shift work or with very  
8 young children would be small. Sixthly, the FSS explored fatigue during the previous week  
9 while the ISI score explored the sleep during the previous month. Hence, it is possible that the  
10 time association between the two variables might not be optimal. Still, as the FSS lies within  
11 the period encompassed by the ISI, we believe that the associations obtained are clinically  
12 relevant. Seventhly, the study is limited to the population of aged 45 to 86, and its  
13 generalizability remains to be assessed. For instance, no information was collected regarding  
14 other confounders among younger subjects, where prevalence of fatigue might be higher due  
15 to parental and professional duties.<sup>48</sup> Finally, possible biases related to the self-reporting of  
16 fatigue could not be avoided, such as over- or under-estimation of symptoms or  
17 misunderstanding of what the term “fatigue” meant; still, this dilution bias would lead to a  
18 decrease in the strength of the associations, and it would be too restrictive in our opinion to  
19 provide a definition of the term “fatigue” to the participants, as different interpretations of the  
20 definition itself could also occur.

## 41 **CONCLUSION**

42  
43  
44 In a population-based sample, fatigue was present in one out of five subjects aged 45  
45 to 86. The major factors associated with fatigue were obesity, insomnia, depression, anemia  
46 and antidepressant medication. The results should be interpreted taking into account the high  
47 exclusion rate.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## **FUNDING**

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401). The funding sources had no involvement in the study design, data collection, analysis and interpretation, writing of the report, or decision to submit the article for publication.

## **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-psycholaus.ch/> for information on how to submit an application for gaining access to CoLaus data.

## **ACKNOWLEDGEMENTS**

Not applicable.

## REFERENCES

1. Mota DD, Pimenta CA. Self-report instruments for fatigue assessment: a systematic review. *Res Theory Nurs Pract* 2006;20(1):49-78. [published Online First: 2006/03/21]
2. Pawlikowska T, Chalder T, Hirsch SR, et al. Population based study of fatigue and psychological distress. *BMJ* 1994;308(6931):763-6. [published Online First: 1994/03/19]
3. Guessous I, Favrat B, Cornuz J, et al. [Fatigue: review and systematic approach to potential causes]. *Rev Med Suisse* 2006;2(89):2725-31. [published Online First: 2007/02/16]
4. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. *J Epidemiol Community Health* 1992;46(2):92-7. [published Online First: 1992/04/01]
5. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. *Psychol Med* 1995;25(5):895-905. [published Online First: 1995/09/01]
6. Bultmann U, Kant I, Kasl SV, et al. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. *J Psychosom Res* 2002;52(6):445-52. [published Online First: 2002/06/19]
7. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;56(2):157-70. doi: 10.1016/S0022-3999(03)00371-4 [published Online First: 2004/03/16]
8. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;45(1):53-65. [published Online First: 1998/08/28]
9. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. [published Online First: 1989/10/01]
10. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006;174(6):765-7. doi: 10.1503/cmaj.1031153 [published Online First: 2006/03/15]
11. Reid S, Chalder T, Cleare A, et al. Chronic fatigue syndrome. *BMJ* 2000;320(7230):292-6. [published Online First: 2000/01/29]
12. Cullen W, Kearney Y, Bury G. Prevalence of fatigue in general practice. *Ir J Med Sci* 2002;171(1):10-2. [published Online First: 2002/05/08]

- 1  
2  
3 13. Basu N, Yang X, Luben RN, et al. Fatigue is associated with excess mortality in the general  
4 population: results from the EPIC-Norfolk study. *BMC Med* 2016;14(1):122. doi:  
5 10.1186/s12916-016-0662-y [published Online First: 2016/08/21]  
6  
7  
8  
9 14. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome  
10 in a primary care practice. *Arch Intern Med* 1993;153(24):2759-65. [published Online First:  
11 1993/12/27]  
12  
13  
14 15. Fieo RA, Mortensen EL, Lund R, et al. Assessing fatigue in late-midlife: increased scrutiny of  
15 the Multiple Fatigue Inventory-20 for community-dwelling subjects. *Assessment*  
16 2014;21(6):706-12. doi: 10.1177/1073191114541143 [published Online First: 2014/07/06]  
17  
18  
19 16. Engberg I, Segerstedt J, Waller G, et al. Fatigue in the general population- associations to  
20 age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the  
21 northern Sweden MONICA study 2014. *BMC Public Health* 2017;17(1):654. doi:  
22 10.1186/s12889-017-4623-y [published Online First: 2017/08/16]  
23  
24  
25 17. Watt T, Groenvold M, Bjorner JB, et al. Fatigue in the Danish general population. Influence of  
26 sociodemographic factors and disease. *J Epidemiol Community Health* 2000;54(11):827-33.  
27 [published Online First: 2000/10/12]  
28  
29  
30 18. David A, Pelosi A, McDonald E, et al. Tired, weak, or in need of rest: fatigue among general  
31 practice attenders. *BMJ* 1990;301(6762):1199-202. [published Online First: 1990/11/24]  
32  
33  
34 19. Lerdal A, Wahl A, Rustoen T, et al. Fatigue in the general population: a translation and test of  
35 the psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J*  
36 *Public Health* 2005;33(2):123-30. doi: 10.1080/14034940410028406 [published Online First:  
37 2005/04/13]  
38  
39  
40 20. Boter H, Manty M, Hansen AM, et al. Self-reported fatigue and physical function in late mid-  
41 life. *J Rehabil Med* 2014;46(7):684-90. doi: 10.2340/16501977-1814 [published Online First:  
42 2014/05/14]  
43  
44  
45 21. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie* 2003;26(2):140-4.  
46 doi: 10.1159/000069834 [published Online First: 2003/05/29]  
47  
48  
49 22. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to  
50 investigate the epidemiology and genetic determinants of cardiovascular risk factors and  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 metabolic syndrome. *BMC Cardiovasc Disord* 2008;8:6. doi: 10.1186/1471-2261-8-6  
4  
5 [published Online First: 2008/03/28]  
6  
7 23. Valko PO, Bassetti CL, Bloch KE, et al. Validation of the fatigue severity scale in a Swiss  
8 cohort. *Sleep* 2008;31(11):1601-7. [published Online First: 2008/11/19]  
9  
10 24. Laranjeira CA. Translation and adaptation of the fatigue severity scale for use in Portugal.  
11 *Appl Nurs Res* 2012;25(3):212-7. doi: 10.1016/j.apnr.2010.11.001 [published Online First:  
12 2012/06/16]  
13  
14 25. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome  
15 measure for insomnia research. *Sleep Med* 2001;2(4):297-307. [published Online First:  
16 2001/07/05]  
17  
18 26. LS R. The CES-D Scale: A Self-Report Depression Scale for Research in the General  
19 Population. *Applied Psychological Measurement* 1977;1((3)):385-401.  
20  
21 27. FR RF. The French version of the CES-D (Center for Epidemiologic Studies-Depression  
22 Scale). *European Psychiatry* 1989;4(3):163-66.  
23  
24 28. Hamieh N, Meneton P, Wiernik E, et al. Depression, treatable cardiovascular risk factors and  
25 incident cardiac events in the Gazel cohort. *Int J Cardiol* 2018 doi:  
26 10.1016/j.ijcard.2018.10.013 [published Online First: 2018/10/12]  
27  
28 29. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of  
29 Confounding in Observational Studies. *Multivariate Behav Res* 2011;46(3):399-424. doi:  
30 10.1080/00273171.2011.568786 [published Online First: 2011/08/06]  
31  
32 30. Luca G, Haba Rubio J, Andries D, et al. Age and gender variations of sleep in subjects  
33 without sleep disorders. *Ann Med* 2015;47(6):482-91. doi: 10.3109/07853890.2015.1074271  
34 [published Online First: 2015/08/01]  
35  
36 31. Ludwig C, Cavalli S, Oris M. "Vivre/Leben/Vivere": An interdisciplinary survey addressing  
37 progress and inequalities of aging over the past 30 years in Switzerland. *Arch Gerontol*  
38 *Geriatr* 2014;59(2):240-8. doi: 10.1016/j.archger.2014.04.004 [published Online First:  
39 2014/05/24]  
40  
41 32. no authors listed. Qualité de vie des seniors en Suisse. In: Centre interfacultaire de  
42 gérontologie et d'études des vulnérabilités, Pôle de Recherche National LIVES, eds. Geneva,  
43 Switzerland: University of Geneva, 2015:4.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 33. Resnick HE, Carter EA, Aloia M, et al. Cross-sectional relationship of reported fatigue to  
4 obesity, diet, and physical activity: results from the third national health and nutrition  
5 examination survey. *J Clin Sleep Med* 2006;2(2):163-9. [published Online First: 2007/06/15]  
6  
7  
8  
9 34. Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population  
10 sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol*  
11 *Metab* 2005;90(8):4510-5. doi: 10.1210/jc.2005-0035 [published Online First: 2005/06/09]  
12  
13  
14 35. Marques-Vidal P, Bochud M, Bastardot F, et al. Association between inflammatory and  
15 obesity markers in a Swiss population-based sample (CoLaus Study). *Obes Facts*  
16 2012;5(5):734-44. doi: 10.1159/000345045 [published Online First: 2012/10/31]  
17  
18  
19 36. Vgontzas AN, Bixler EO, Chrousos GP. Obesity-related sleepiness and fatigue: the role of the  
20 stress system and cytokines. *Ann N Y Acad Sci* 2006;1083:329-44. doi:  
21 10.1196/annals.1367.023 [published Online First: 2006/12/07]  
22  
23  
24 37. Kallestad H, Jacobsen HB, Landro NI, et al. The role of insomnia in the treatment of chronic  
25 fatigue. *J Psychosom Res* 2015;78(5):427-32. doi: 10.1016/j.jpsychores.2014.11.022  
26  
27 [published Online First: 2014/12/17]  
28  
29  
30 38. Pires ML, Benedito-Silva AA, Mello MT, et al. Sleep habits and complaints of adults in the city  
31 of Sao Paulo, Brazil, in 1987 and 1995. *Braz J Med Biol Res* 2007;40(11):1505-15. [published  
32 Online First: 2007/10/16]  
33  
34  
35 39. Lawrie SM, Manders DN, Geddes JR, et al. A population-based incidence study of chronic  
36 fatigue. *Psychol Med* 1997;27(2):343-53. [published Online First: 1997/03/01]  
37  
38  
39 40. Wessely S, Chalder T, Hirsch S, et al. Psychological symptoms, somatic symptoms, and  
40 psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in  
41 the primary care setting. *Am J Psychiatry* 1996;153(8):1050-9. doi: 10.1176/ajp.153.8.1050  
42  
43 [published Online First: 1996/08/01]  
44  
45  
46 41. Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic  
47 fatigue and psychiatric morbidity: results from a community survey in Great Britain. *Int Rev*  
48 *Psychiatry* 2003;15(1-2):57-64. doi: 10.1080/0954026021000045958 [published Online First:  
49 2003/05/15]  
50  
51  
52 42. Powell R, Dolan R, Wessely S. Attributions and self-esteem in depression and chronic fatigue  
53 syndromes. *J Psychosom Res* 1990;34(6):665-73. [published Online First: 1990/01/01]  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 43. Harvey SB, Wessely S, Kuh D, et al. The relationship between fatigue and psychiatric  
4 disorders: evidence for the concept of neurasthenia. *J Psychosom Res* 2009;66(5):445-54.  
5  
6 doi: 10.1016/j.jpsychores.2008.12.007 [published Online First: 2009/04/22]  
7  
8  
9 44. Christian LM, Glaser R, Porter K, et al. Poorer self-rated health is associated with elevated  
10 inflammatory markers among older adults. *Psychoneuroendocrinology* 2011;36(10):1495-504.  
11  
12 doi: 10.1016/j.psyneuen.2011.04.003 [published Online First: 2011/05/24]  
13  
14 45. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive  
15 minimal clinically important differences on the Functional Assessment of Cancer Therapy  
16 (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;24(6):547-61. [published  
17  
18 Online First: 2003/01/29]  
19  
20 46. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the  
21 general United States population. *Cancer* 2002;94(2):528-38. doi: 10.1002/cncr.10245  
22  
23 [published Online First: 2002/03/20]  
24  
25 47. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study.  
26  
27 *Arch Intern Med* 2000;160(4):526-34. [published Online First: 2000/03/01]  
28  
29 48. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial  
30 factors relating to fatigue in men and women. *Med Care* 1999;37(10):1078-83. [published  
31  
32 Online First: 1999/10/19]  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## 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 entraînent 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

Annexes

## 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

## Annexes

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

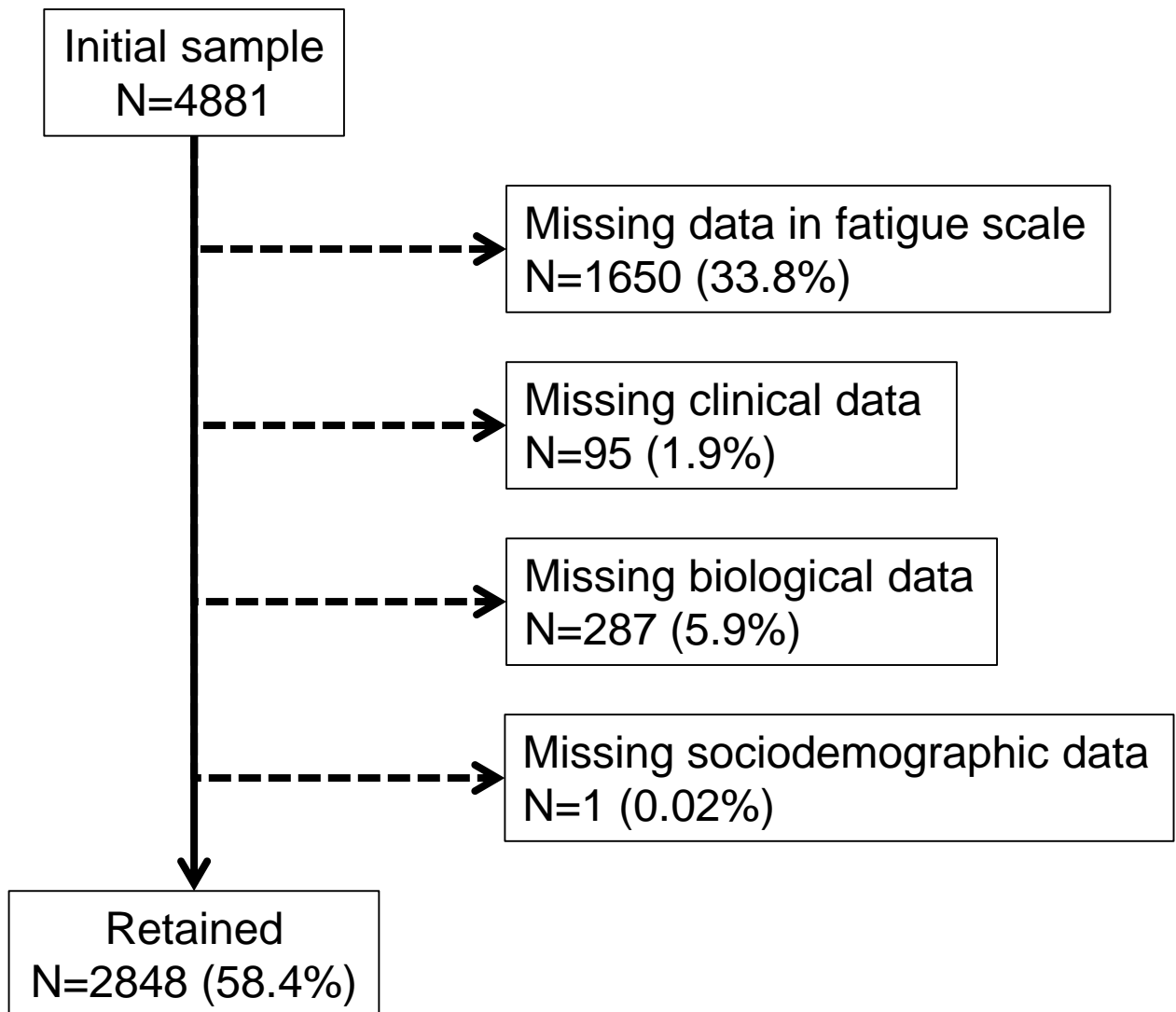
Pour analyser et interpréter ce questionnaire, additionnez les notes données aux questions 4a, 4b, 4c, 5, 6, 7 et 8.  
Le score total s'établit entre 0 et 28.

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

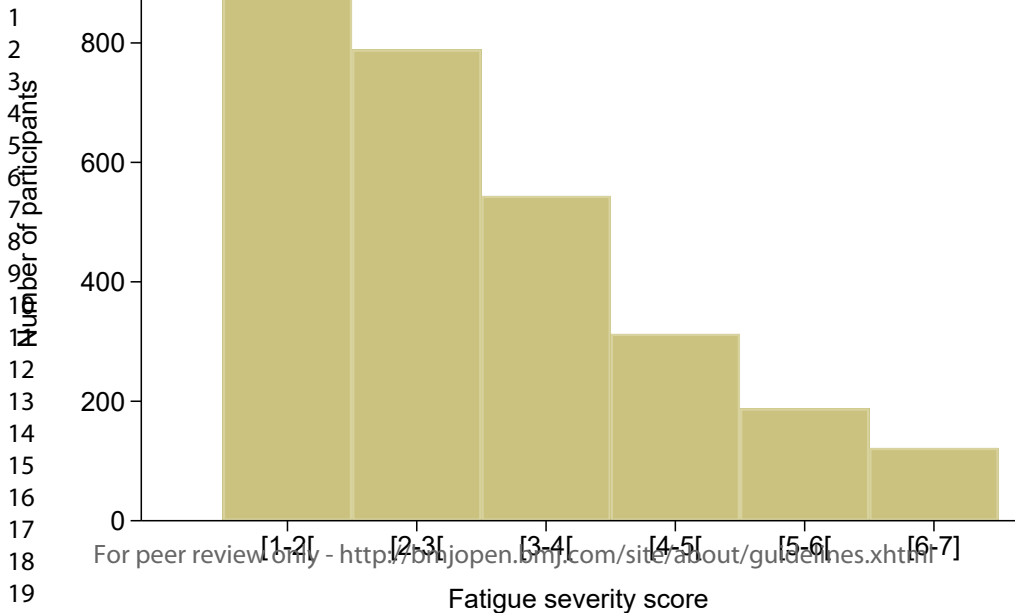
## Référence

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 <sup>2</sup> )	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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



**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  $\geq 5$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

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

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average  $\pm$  standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average  $\pm$  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  $\geq 5$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate		p-value	Multivariable model 1		Multivariable model 2	
	No fatigue	Fatigue		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)		-		-	

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

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  $\geq 4$  of the fatigue severity scale, while model 2 included only the variables significantly ( $p < 0.05$ ) associated with fatigue using the threshold of  $\geq 5$  of the fatigue severity scale.

**Supplemental table 5:** Multivariable analysis of the categorical determinants of fatigue (defined as a fatigue severity score  $\geq 4$ ) 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027070.R2
Article Type:	Research
Date Submitted by the Author:	11-Jun-2019
Complete List of Authors:	Galland, Coralie; Centre Hospitalier Universitaire Vaudois, Médecine Marques-Vidal, Pedro; Lausanne University Hospital, Department of Internal Medicine Vollenweider, Peter; Lausanne University Hospital, Internal Medicine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	General practice / Family practice
Keywords:	fatigue, prevalence, fatigue severity scale, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3 **Prevalence and factors associated with fatigue in the Lausanne**  
4 **middle-aged population: A population based cross-sectional**  
5 **survey**  
6

7 Coralie Galland-Decker, Pedro Marques-Vidal and Peter Vollenweider  
8  
9

10 Department of Medicine, Internal Medicine, Lausanne university hospital, Lausanne,  
11  
12 Switzerland  
13  
14

15 **Authors' emails:**

16 Coralie Galland-Decker: [Coralie.Galland@chuv.ch](mailto:Coralie.Galland@chuv.ch)

17 Pedro Marques-Vidal: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)

18 Peter Vollenweider: [Peter.Vollenweider@chuv.ch](mailto:Peter.Vollenweider@chuv.ch)  
19  
20  
21  
22

23 **Address for correspondence and reprints**

24 Pedro Marques-Vidal

25 Office BH10-642.

26 Department of Medicine, Internal Medicine.

27 Lausanne university hospital.

28 Rue du Bugnon 46, 1011, Lausanne, Switzerland.

29 Phone: +41 21 314 09 34

30 Email: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)  
31  
32  
33  
34  
35  
36  
37

38 **Word count:** 4571  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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  $\geq 4$  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.

1  
2  
3 **Keywords:** fatigue; prevalence; epidemiology; Fatigue severity scale  
4  
5

6 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
7

- 8 - This study assessed the prevalence and factors associated with fatigue in a general  
9 population setting.  
10  
11 - A large panel of associated with fatigue was evaluated.  
12  
13 - A list of the most frequent determinants was established, facilitating etiological  
14 search in clinical practice  
15  
16 - The study was limited to subjects aged 45 to 86, so results do not apply to younger  
17 or older groups.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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”.<sup>1</sup>

Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities.

<sup>1</sup> Indeed, fatigue is a common symptom with prevalence rates varying between 4 and 45%.<sup>2-</sup>

<sup>4</sup> This ten-fold range in prevalence rates is likely due to the different settings (i.e. general practice<sup>5</sup> or workers<sup>6</sup>) or the different methods used to assess fatigue.<sup>7</sup>

In healthy subjects, tiredness or sleepiness are a natural occurrence after physical or mental efforts, and are usually relieved by rest.<sup>8-9</sup> While fatigue is defined as extreme and persistent tiredness, weakness or exhaustion, of mental and/or physical origin<sup>7</sup> that is not relieved by rest. Fatigue is defined in duration as recent (<1 month) prolonged (1 to 6 months) and chronic (>6 months)<sup>10</sup>. 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)<sup>11</sup> or as idiopathic (absence of other symptoms).

Fatigue is one of the most common complaints reported in primary care<sup>12</sup> and is associated with a decreased quality of life and increased morbidity and mortality in the general population.<sup>13</sup> 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.<sup>10</sup> 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.<sup>14</sup> Fatigue has also been associated with female sex,<sup>8-15</sup> older age<sup>16-17</sup> and lower socioeconomic status,<sup>16-17</sup> although the association with the last two determinants were not found in some studies.<sup>8-18</sup> Importantly, most studies on fatigue have been conducted in selected populations such as workers<sup>6</sup> or general practice attendees.<sup>2-5-18</sup> To our knowledge, only two studies have assessed the prevalence of fatigue in the general population<sup>8-19</sup> and only a few have explored the

1  
2  
3 determinants of fatigue in the general population.<sup>13 15-17 20 21</sup> Furthermore, most studies focused  
4 on socio-economic and disease determinants of fatigue, while information regarding the  
5 biological determinants (i.e. anemia or thyroid pathology)<sup>13</sup> or the medications associated with  
6 fatigue is scarce. Moreover, to date, little is known about the prevalence of fatigue and its  
7 determinants in Switzerland.  
8  
9  
10  
11  
12

13  
14 Hence, this study aimed to examine the prevalence and the factors associated with  
15 fatigue in a population-based sample from the city of Lausanne, Switzerland.  
16  
17

## 18 19 **POPULATION AND METHODS**

### 20 21 **Study population**

22  
23 The CoLaus study is a population-based cohort exploring biological, genetic, and  
24 environmental determinants of cardiovascular diseases. Detailed descriptions of the study  
25 design have been reported elsewhere.<sup>22</sup> Briefly, a non-stratified random representative  
26 sample of the population of Lausanne was recruited between 2003 and 2006 using the  
27 following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate.  
28 The first follow-up was performed between April 2009 and September 2012 and the second  
29 follow-up between May 2014 and April 2017, 10.9 years on average after the baseline study.  
30 At both baseline and subsequent follow-ups, participants were invited to attend a clinical  
31 examination at the Lausanne university hospital. Participants received a paper questionnaire  
32 at home, which they filled prior to the clinical examination. During the clinical examination, a  
33 second questionnaire regarding personal and family history of cardiovascular disease and  
34 cardiovascular risk factors was applied. For more details, please consult [www.colaus-psycolaus.ch](http://www.colaus-psycolaus.ch).  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50

51  
52 As fatigue was only assessed in the second follow-up, data from the second follow-up,  
53 which included 4881 of the initial 6773 participants recruited at baseline, was used. At the  
54 second follow-up, participants were aged 45-86 years.  
55  
56  
57  
58  
59  
60

## Fatigue scale

Fatigue severity during the previous week was assessed by the 9 items Fatigue Severity Scale (FSS).<sup>9</sup> The FSS is one of the most commonly used fatigue questionnaires. It had been validated in a healthy population setting in German-speaking Switzerland<sup>23</sup>, Portugal<sup>24</sup> and Norway<sup>19</sup>. It is a simple, time-saving, self-administrated questionnaire allowing its use in large epidemiological studies and has a high test-retest reliability.<sup>7</sup> 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  $\geq 4$  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.<sup>9</sup> 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).<sup>25</sup> 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

1  
2  
3 global ISI score (range: 0-28). The questionnaire is provided in **Annex 3**. Clinically significant  
4 insomnia was defined as an ISI score  $\geq 15$  (moderate to severe intensity).<sup>25</sup>  
5  
6

7  
8 Depression was assessed with the CES-D <sup>26</sup>, a 20 item self-report instrument,  
9 developed for research in the general population, that is used to assess the severity of  
10 depressive symptoms over the past week on a 4-point scale. It was translated into French by  
11 Fuhrer and Rouillon.<sup>27</sup> It has been used in other recent epidemiological studies assessing the  
12 link between depression and cardiovascular risk factors <sup>28</sup>. The questionnaire is composed of  
13 20 questions; responses are graded from 0 to 3, where 0 indicates rarely or never (less than  
14 one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the  
15 20 responses (possible range is 0-60), and a score  $\geq 16$  is considered as a risk for depression.  
16  
17  
18  
19  
20  
21  
22  
23  
24

25 Self-rated health was assessed by a single question where participants had to rate  
26 their current health status from five categories ranging from “very bad” to “very good”. As the  
27 number of participants rating their health as “very bad” was very small, they were grouped with  
28 the participants who rated their health as “bad”.  
29  
30  
31  
32  
33

34 Body weight and height were measured with participants standing without shoes in  
35 light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™  
36 scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™  
37 height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as  
38 weight/height<sup>2</sup> and categorized as underweight (BMI < 18.5 kg/m<sup>2</sup>), normal (18.5 ≤ BMI < 25  
39 kg/m<sup>2</sup>); overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>) and obese (BMI ≥ 30 kg/m<sup>2</sup>).  
40  
41  
42  
43  
44  
45  
46

47 Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer  
48 (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted  
49 and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and  
50 30° of dorsiflexion. Three measurements were performed consecutively with the right hand  
51 and the highest value (expressed in kg) was included in the analyses.  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 Caffeinated drink consumption was assessed by the question “How many cups or cans  
4 of drinks containing caffeine (coffee, tea, coke or similar) do you drink per day?” with possible  
5 answers “None”, “1-3”, “4-6” and “7 or more”.  
6  
7  
8

9  
10 Participants were asked to report all medications (prescribed or bought over the  
11 counter) they took during the last 6 months. Medications were coded using the Anatomical,  
12 Therapeutic Chemical (ATC) classification of the world health organization  
13 ([www.whooc.no/atc\\_ddd\\_index/](http://www.whooc.no/atc_ddd_index/)). Antihistamics were defined as any ATC code beginning with  
14 “R06”; antidepressants were defined as an ATC code beginning with “N05BD” or “N06AA” or  
15 “N06AB” or “N06AF” or “N06AG” or “N06AX” or “N06CA”; hypnotics were defined as any ATC  
16 code beginning with “N05C”. Antihypertensive drugs were defined by asking the participants  
17 if they were taking drugs for hypertension.  
18  
19  
20  
21  
22  
23  
24  
25

26  
27 Diabetes was defined by a fasting plasma glucose  $\geq 7$  mmol/L and/or the presence of  
28 an antidiabetic drug treatment (oral or insulin). Personal history of cardio vascular disease was  
29 assessed by asking the participant if he/she had sustained a coronary event (myocardial  
30 infarction or angina pectoris) or a stroke.  
31  
32  
33  
34  
35

36 Biological assays were performed by the CHUV Clinical Laboratory on fresh blood  
37 samples within 2 hours of blood collection, and additional aliquots were stored at  $-80^{\circ}\text{C}$ . All  
38 measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland).  
39 The following analytical procedures (with maximum inter and intra-batch CVs) were used: high  
40 sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay  
41 (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by  
42 immunoturbidimetric method (Tina-quant 4<sup>th</sup> generation, Roche Diagnostics, Switzerland) with  
43 a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid  
44 stimulating hormone (TSH) and free  $T_4$  were assessed by chemiluminescence (ECLIA) on a  
45 Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs  
46 ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free  $T_4$ .  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 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](http://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.

1  
2  
3 Sensitivity analyses were conducted using a FSS threshold of 5. Further, as the  
4 number of excluded participants was high, other sensitivity analyses were conducted by  
5 creating a propensity score for being excluded<sup>29</sup>. The propensity score was computed using  
6 logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly  
7 associated with exclusion as independent variables. A probability of exclusion was computed  
8 for each participant, and the inverse of the probability was used for weighting.  
9  
10  
11  
12  
13  
14  
15

16 Statistical significance was assessed for a two-sided test with  $p < 0.05$ .  
17  
18

## 19 **RESULTS**

### 20 **Study population**

21  
22 Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for  
23 analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most  
24 frequent reason was lack of data regarding fatigue. The comparison between included and  
25 excluded participants is provided in **supplemental table 1** and the results of the multivariable  
26 analysis are provided in **supplemental table 2**. Excluded participants were more frequently  
27 women, were older, had a lower educational level, were more frequently never or current  
28 smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and  
29 hypertension) and rated their health worse.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

### 44 **Prevalence and factors associated with fatigue**

45  
46 The overall prevalence of fatigue as defined by a FSS  $\geq 4$  was 21.9% (95% CI: 20.4%  
47 – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% -  
48 22.3%),  $p = 0.031$ . The distribution of the FSS  $\geq 5$  (prevalence of fatigue 10.9%) is provided in  
49 **supplemental figure 2**; the number of participants with fatigue decreased when the levels of  
50 FSS increased.  
51  
52  
53  
54  
55

56  
57 The analysis of the factors associated with fatigue as defined by a FSS  $\geq 4$  is provided  
58 in **Tables 1 and 2**.  
59  
60

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

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

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average  $\pm$  standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average  $\pm$  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  $\geq 4$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate		p-value	Multivariable	
	No fatigue	Fatigue		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)	

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

1  
2  
3 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend  
4 <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively  
5 associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-  
6 histaminics or hypnotics (**Table 2**).

### 11 **Sensitivity analyses**

12  
13  
14 The overall prevalence of fatigue as defined by a FSS  $\geq 5$  was 10.9% (95% CI: 9.7% –  
15 12.1%) and was higher in women 12.3% (10.7% - 14.0%) than in men 9.3% (7.8% - 11.1%),  
16 p=0.011. The results of the sensitivity analyses using a FSS threshold of  $\geq 5$  are provided in  
17 **supplemental tables 3 and 4**. Overall, the results were comparable with those using a  
18 threshold of  $\geq 4$ : gender, insomnia categories (p-value for trend <0.001), and low self-rated  
19 health status (p-value for trend <0.001) were positively associated with fatigue. Conversely,  
20 no association was found for age, obesity, diabetes, TSH levels, antihistaminics,  
21 antidepressives or hypnotics (**supplemental table 4**).

22  
23  
24 Sensitivity analysis using inverse probability weighting by the propensity score led to  
25 similar findings, except that anemia and antidepressants were no longer associated with  
26 fatigue, while a positive association was found between low TSH levels and fatigue  
27 (**Supplemental table 5**).

### 31 **DISCUSSION**

32  
33  
34 To our knowledge, this is one of the few studies assessing the prevalence and the  
35 factors associated with fatigue in a general population setting, and the first study conducted  
36 in Switzerland. Using a FSS cut-off  $\geq 4$ , our results indicate that one out of five people aged  
37 between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and  
38 decreasing self-rated health status were positively associated with fatigue; while older age  
39 was negatively associated with fatigue.

### Prevalence of fatigue

Using the cut-off of  $\geq 4$ , fatigue was present in one out of five participants (22.1%), a finding in agreement with the study by Loge et al.<sup>8</sup>, which reported a prevalence of 22% among 2323 participants using the Chalder fatigue scale. Conversely, the cross-sectional study by Lerdal et al.<sup>19</sup>, 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  $\geq 4$  and  $\geq 5$  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,<sup>2</sup> whereas a study conducted in the Dutch working population reported a prevalence of fatigue of 22% using other fatigue measures.<sup>6</sup> 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<sup>8 15</sup> but not in others.<sup>18</sup> In a Swedish study conducted in 2014, Engberg et al.<sup>16</sup> 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.<sup>16</sup> Similarly, a previous study found that older subjects complain less of sleepiness.<sup>30</sup> Still, this association was no longer statistically significant when the cut off of  $\geq 5$  was applied to define fatigue, suggesting that young subjects



1  
2  
3 tend to present with borderline fatigue as suggested previously<sup>19</sup>. Conversely, earlier studies  
4 (1990-2000) found a positive association between age and fatigue.<sup>8 17 21</sup> A possible  
5 explanation for this difference is that older people might have a better quality of life nowadays  
6 and are less depressed. Although there is little information regarding trends in quality of life  
7 among Swiss elderly, the VLV study<sup>31</sup> concluded that quality of life among Swiss elderly  
8 increased in the last 30 years<sup>32</sup>. Indeed, in our study, the lowest prevalence of fatigue was  
9 reported by participants aged 64-74 years, which are the “young” retired with few  
10 comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger  
11 participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and  
12 12.5% in the 45-54 and 55-64 years, respectively, p-value<0.001).

13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Obese subjects had a higher prevalence of fatigue defined by a FSS  $\geq 4$ . This finding  
is in agreement with studies conducted in the USA<sup>33</sup> and in the UK.<sup>13</sup> . Still, this association  
was no longer statistically significant when the cut off of  $\geq 5$  was applied to define fatigue,  
suggesting that obese subjects tend to present with borderline fatigue as suggested previously<sup>19</sup>.  
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.<sup>34</sup> 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,<sup>35</sup> which would lead to higher fatigue,<sup>36</sup> 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<sup>34</sup> and a Norwegian study conducted in 2014 showed  
that reducing insomnia severity led to a concomitant reduction in fatigue.<sup>37</sup> Interestingly, many  
subjects with sleep complaints do not consult for this issue,<sup>38</sup> which might lead to an

1  
2  
3 underestimation of its prevalence. Overall, our results suggest that insomnia is an important  
4 and underestimated factor of fatigue.  
5  
6  
7

8 Both depression and antidepressant medication were independently and positively  
9 associated with fatigue. The association between depression and fatigue has been  
10 repeatedly reported,<sup>13 39-41</sup> and the same applies for antidepressant medication.<sup>3</sup> Our  
11 results confirm the known association between depression and fatigue, and suggest that  
12 antidepressant treatment might not systematically relieve fatigue among depressive  
13 subjects. Furthermore, fatigue is a common side effect of antidepressant therapy and a  
14 symptom of depression, making the identification of the cause of fatigue difficult with a  
15 possibility of reverse causality (fatigue leading to depression and vice versa). We used a  
16 one-dimensional tool to evaluate fatigue (FSS); hence, we cannot distinguish between  
17 physical and mental fatigue. There is considerable overlap in phenomenology of fatigue  
18 and depression or anxiety but there are some important differences. People with fatigue  
19 without psychiatric symptoms tend to attribute their symptoms to external causes.  
20 Conversely, most depressed people experience self-blame or lowered self-esteem <sup>42</sup>.  
21 Further, fatigue and depression commonly appear together. A study conducted in 2009 by  
22 Harvey et al. <sup>43</sup>, showed that 7% of fatigued persons have no psychiatric symptoms, but  
23 remained at increased risk of later psychiatric disorder independently of the severity of  
24 fatigue.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

44 A strong association was found between poor self-rated health and fatigue, a finding  
45 also reported elsewhere.<sup>6 16</sup> Low self-rated health has been associated with increased levels  
46 of inflammatory markers such as interleukin 6 and CRP,<sup>44</sup> which in turn could trigger fatigue.  
47 Conversely, increased fatigue might lead to a lower rating of health status.  
48  
49  
50  
51  
52

### 53 **Biological factors associated with fatigue**

54  
55 Participants with anemia had a higher likelihood of reporting fatigue. This finding is in  
56 agreement with the literature,<sup>45 46</sup> although no association between fatigue and low  
57 haemoglobin levels was found in a UK study. <sup>13</sup> A possible explanation is that in the UK study,  
58  
59  
60

1  
2  
3 anemia was defined as a hemoglobin <110 g/l, which is lower than the thresholds used in our  
4 study (<133 g/l for men and <117 g/l for women). This led to a small sample size (356  
5 participants, corresponding to 1.9% of the overall sample) and thus a low statistical power.  
6  
7  
8

9  
10 Hypothyroidism is often cited during the investigation of fatigue.<sup>10</sup> In this study  
11 participants with low TSH levels reported fatigue more frequently, but this association was  
12 significant only after multivariable analysis with inverse probability weighting. Furthermore, the  
13 prevalence of low TSH levels was <1% in the overall sample. The associations between  
14 hypothyroidism and fatigue have been controversial for a long time.<sup>10</sup> Basu et al. found no  
15 association between TSH categories and fatigue<sup>13</sup> and Canaris et al<sup>47</sup> reported that the  
16 association between fatigue and hypothyroidism was weak. Overall, our results suggest that,  
17 in presence of fatigue, hypothyroidism is an unlikely cause and should not be systematically  
18 assessed.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

### 29 **Implications of the study**

30  
31 Based on our study findings, we propose to focus on specific clinical and biological  
32 factors amenable to treatment at an individual level. Regarding clinical factors, sleep  
33 disturbances such as insomnia and sleep apnea (namely in presence of a patient with obesity)  
34 and the presence of depression should be assessed. Hence, lifestyle measures to improve  
35 sleep quality and quantity should be preferred to medication.<sup>22</sup> In the case of depression, it  
36 will be important to warn patients that antidepressor medication might not necessarily lead into  
37 rapid relief of fatigue. Regarding biological factors, anemia should be ruled out, while  
38 screening for hypothyroidism is not recommended as a first step.  
39  
40  
41  
42  
43  
44  
45  
46  
47

48 At the population level, preventive measures such as stress management and health  
49 promotion like relaxation, time management and cognitive reframing (for example within the  
50 work environment) could improve sleep quality, increase self-rated health<sup>48</sup> and consequently  
51 reduce fatigue.  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 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).<sup>3</sup> 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,

1  
2  
3 no information was available regarding shift work or the presence of very young children. Still,  
4 as a sizable fraction (almost 70%) of the sample was aged over 55 and over 36% of the sample  
5 was aged over 64, it is likely that the number of participants either on shift work or with very  
6 young children would be small. Sixthly, the FSS explored fatigue during the previous week  
7 while the ISI score explored the sleep during the previous month. Hence, it is possible that the  
8 time association between the two variables might not be optimal. Still, as the FSS lies within  
9 the period encompassed by the ISI, we believe that the associations obtained are clinically  
10 relevant. Seventhly, the study is limited to the population of aged 45 to 86, and its  
11 generalizability remains to be assessed. For instance, no information was collected regarding  
12 other confounders among younger subjects, where prevalence of fatigue might be higher due  
13 to parental and professional duties.<sup>49</sup> Finally, possible biases related to the self-reporting of  
14 fatigue could not be avoided, such as over- or under-estimation of symptoms or  
15 misunderstanding of what the term “fatigue” meant; still, this dilution bias would lead to a  
16 decrease in the strength of the associations, and it would be too restrictive in our opinion to  
17 provide a definition of the term “fatigue” to the participants, as different interpretations of the  
18 definition itself could also occur.

### 36 37 **Recommendations for future studies**

38  
39 Future studies on the prevalence of fatigue in the general population should focus on  
40 the following topics: 1) validate the questionnaires in the population of interest; 2) whenever  
41 possible, use a standardised questionnaire to allow comparison between studies.

42  
43 While some factors such as obesity <sup>13 33</sup>, depression <sup>13 39-41</sup> and antidepressor  
44 medications <sup>3</sup> were consistently associated with fatigue in our study and in the literature,  
45 controversial findings such as the association between fatigue and gender, age groups and  
46 anemia should be further explored.

### 54 55 **CONCLUSION**

56  
57 In a population-based sample, fatigue was present in one out of five subjects aged 45  
58 to 86. The major factors associated with fatigue were obesity, insomnia, depression, anemia  
59  
60

1  
2  
3 and antidepressant medication. The results should be interpreted taking into account the high  
4  
5 exclusion rate.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## **FUNDING**

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401). The funding sources had no involvement in the study design, data collection, analysis and interpretation, writing of the report, or decision to submit the article for publication.

## **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-psycholaus.ch/> for information on how to submit an application for gaining access to CoLaus data.

## **ACKNOWLEDGEMENTS**

Not applicable.

**REFERENCES**

1. Mota DD, Pimenta CA. Self-report instruments for fatigue assessment: a systematic review. *Res Theory Nurs Pract* 2006;20(1):49-78. [published Online First: 2006/03/21]
2. Pawlikowska T, Chalder T, Hirsch SR, et al. Population based study of fatigue and psychological distress. *BMJ* 1994;308(6931):763-6. [published Online First: 1994/03/19]
3. Guessous I, Favrat B, Cornuz J, et al. [Fatigue: review and systematic approach to potential causes]. *Rev Med Suisse* 2006;2(89):2725-31. [published Online First: 2007/02/16]
4. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. *J Epidemiol Community Health* 1992;46(2):92-7. [published Online First: 1992/04/01]
5. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. *Psychol Med* 1995;25(5):895-905. [published Online First: 1995/09/01]
6. Bultmann U, Kant I, Kasl SV, et al. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. *J Psychosom Res* 2002;52(6):445-52. [published Online First: 2002/06/19]
7. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;56(2):157-70. doi: 10.1016/S0022-3999(03)00371-4 [published Online First: 2004/03/16]
8. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;45(1):53-65. [published Online First: 1998/08/28]
9. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. [published Online First: 1989/10/01]
10. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006;174(6):765-7. doi: 10.1503/cmaj.1031153 [published Online First: 2006/03/15]
11. Reid S, Chalder T, Cleare A, et al. Chronic fatigue syndrome. *BMJ* 2000;320(7230):292-6. [published Online First: 2000/01/29]
12. Cullen W, Kearney Y, Bury G. Prevalence of fatigue in general practice. *Ir J Med Sci* 2002;171(1):10-2. [published Online First: 2002/05/08]



- 1  
2  
3 13. Basu N, Yang X, Luben RN, et al. Fatigue is associated with excess mortality in the general  
4 population: results from the EPIC-Norfolk study. *BMC Med* 2016;14(1):122. doi:  
5 10.1186/s12916-016-0662-y [published Online First: 2016/08/21]  
6  
7  
8  
9 14. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a  
10 primary care practice. *Arch Intern Med* 1993;153(24):2759-65. [published Online First:  
11 1993/12/27]  
12  
13  
14  
15 15. Fieo RA, Mortensen EL, Lund R, et al. Assessing fatigue in late-midlife: increased scrutiny of the  
16 Multiple Fatigue Inventory-20 for community-dwelling subjects. *Assessment* 2014;21(6):706-  
17 12. doi: 10.1177/1073191114541143 [published Online First: 2014/07/06]  
18  
19  
20  
21 16. Engberg I, Segerstedt J, Waller G, et al. Fatigue in the general population- associations to age,  
22 sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern  
23 Sweden MONICA study 2014. *BMC Public Health* 2017;17(1):654. doi: 10.1186/s12889-017-  
24 4623-y [published Online First: 2017/08/16]  
25  
26  
27  
28 17. Watt T, Groenvold M, Bjorner JB, et al. Fatigue in the Danish general population. Influence of  
29 sociodemographic factors and disease. *J Epidemiol Community Health* 2000;54(11):827-33.  
30 [published Online First: 2000/10/12]  
31  
32  
33  
34 18. David A, Pelosi A, McDonald E, et al. Tired, weak, or in need of rest: fatigue among general  
35 practice attenders. *BMJ* 1990;301(6762):1199-202. [published Online First: 1990/11/24]  
36  
37  
38 19. Lerdal A, Wahl A, Rustoen T, et al. Fatigue in the general population: a translation and test of the  
39 psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J Public*  
40 *Health* 2005;33(2):123-30. doi: 10.1080/14034940410028406 [published Online First:  
41 2005/04/13]  
42  
43  
44  
45 20. Boter H, Manty M, Hansen AM, et al. Self-reported fatigue and physical function in late mid-life. *J*  
46 *Rehabil Med* 2014;46(7):684-90. doi: 10.2340/16501977-1814 [published Online First:  
47 2014/05/14]  
48  
49  
50  
51 21. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie* 2003;26(2):140-4. doi:  
52 10.1159/000069834 [published Online First: 2003/05/29]  
53  
54  
55 22. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate  
56 the epidemiology and genetic determinants of cardiovascular risk factors and metabolic  
57  
58  
59  
60

- 1  
2  
3 syndrome. *BMC Cardiovasc Disord* 2008;8:6. doi: 10.1186/1471-2261-8-6 [published Online  
4 First: 2008/03/28]  
5  
6  
7 23. Valko PO, Bassetti CL, Bloch KE, et al. Validation of the fatigue severity scale in a Swiss cohort.  
8  
9 *Sleep* 2008;31(11):1601-7. [published Online First: 2008/11/19]  
10  
11 24. Laranjeira CA. Translation and adaptation of the fatigue severity scale for use in Portugal. *Appl*  
12  
13 *Nurs Res* 2012;25(3):212-7. doi: 10.1016/j.apnr.2010.11.001 [published Online First:  
14 2012/06/16]  
15  
16 25. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome  
17  
18 measure for insomnia research. *Sleep Med* 2001;2(4):297-307. [published Online First:  
19 2001/07/05]  
20  
21  
22 26. LS R. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population.  
23  
24 *Applied Psychological Measurement* 1977;1((3)):385-401.  
25  
26 27. FR RF. The French version of the CES-D (Center for Epidemiologic Studies-Depression Scale).  
27  
28 *European Psychiatry* 1989;4(3):163-66.  
29  
30 28. Hamieh N, Meneton P, Wiernik E, et al. Depression, treatable cardiovascular risk factors and  
31  
32 incident cardiac events in the Gazel cohort. *Int J Cardiol* 2018 doi:  
33 10.1016/j.ijcard.2018.10.013 [published Online First: 2018/10/12]  
34  
35 29. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding  
36  
37 in Observational Studies. *Multivariate Behav Res* 2011;46(3):399-424. doi:  
38 10.1080/00273171.2011.568786 [published Online First: 2011/08/06]  
39  
40  
41 30. Luca G, Haba Rubio J, Andries D, et al. Age and gender variations of sleep in subjects without  
42  
43 sleep disorders. *Ann Med* 2015;47(6):482-91. doi: 10.3109/07853890.2015.1074271  
44  
45 [published Online First: 2015/08/01]  
46  
47 31. Ludwig C, Cavalli S, Oris M. "Vivre/Leben/Vivere": An interdisciplinary survey addressing progress  
48  
49 and inequalities of aging over the past 30 years in Switzerland. *Arch Gerontol Geriatr*  
50  
51 2014;59(2):240-8. doi: 10.1016/j.archger.2014.04.004 [published Online First: 2014/05/24]  
52  
53 32. no authors listed. Qualité de vie des seniors en Suisse. In: Centre interfacultaire de gérontologie  
54  
55 et d'études des vulnérabilités, Pôle de Recherche National LIVES, eds. Geneva, Switzerland:  
56 University of Geneva, 2015:4.  
57  
58  
59  
60

- 1  
2  
3 33. Resnick HE, Carter EA, Aloia M, et al. Cross-sectional relationship of reported fatigue to obesity,  
4 diet, and physical activity: results from the third national health and nutrition examination  
5 survey. *J Clin Sleep Med* 2006;2(2):163-9. [published Online First: 2007/06/15]  
6  
7  
8  
9 34. Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population  
10 sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol*  
11 *Metab* 2005;90(8):4510-5. doi: 10.1210/jc.2005-0035 [published Online First: 2005/06/09]  
12  
13  
14 35. Marques-Vidal P, Bochud M, Bastardot F, et al. Association between inflammatory and obesity  
15 markers in a Swiss population-based sample (CoLaus Study). *Obes Facts* 2012;5(5):734-44.  
16 doi: 10.1159/000345045 [published Online First: 2012/10/31]  
17  
18  
19 36. Vgontzas AN, Bixler EO, Chrousos GP. Obesity-related sleepiness and fatigue: the role of the  
20 stress system and cytokines. *Ann N Y Acad Sci* 2006;1083:329-44. doi:  
21 10.1196/annals.1367.023 [published Online First: 2006/12/07]  
22  
23  
24 37. Kallestad H, Jacobsen HB, Landro NI, et al. The role of insomnia in the treatment of chronic  
25 fatigue. *J Psychosom Res* 2015;78(5):427-32. doi: 10.1016/j.jpsychores.2014.11.022  
26  
27  
28 [published Online First: 2014/12/17]  
29  
30  
31 38. Pires ML, Benedito-Silva AA, Mello MT, et al. Sleep habits and complaints of adults in the city of  
32 Sao Paulo, Brazil, in 1987 and 1995. *Braz J Med Biol Res* 2007;40(11):1505-15. [published  
33 Online First: 2007/10/16]  
34  
35  
36 39. Lawrie SM, Manders DN, Geddes JR, et al. A population-based incidence study of chronic fatigue.  
37 *Psychol Med* 1997;27(2):343-53. [published Online First: 1997/03/01]  
38  
39  
40 40. Wessely S, Chalder T, Hirsch S, et al. Psychological symptoms, somatic symptoms, and  
41 psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in  
42 the primary care setting. *Am J Psychiatry* 1996;153(8):1050-9. doi: 10.1176/ajp.153.8.1050  
43  
44  
45 [published Online First: 1996/08/01]  
46  
47  
48 41. Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic fatigue  
49 and psychiatric morbidity: results from a community survey in Great Britain. *Int Rev Psychiatry*  
50 2003;15(1-2):57-64. doi: 10.1080/0954026021000045958 [published Online First: 2003/05/15]  
51  
52  
53 42. Powell R, Dolan R, Wessely S. Attributions and self-esteem in depression and chronic fatigue  
54 syndromes. *J Psychosom Res* 1990;34(6):665-73. [published Online First: 1990/01/01]  
55  
56  
57  
58  
59  
60

- 1  
2  
3 43. Harvey SB, Wessely S, Kuh D, et al. The relationship between fatigue and psychiatric disorders:  
4  
5 evidence for the concept of neurasthenia. *J Psychosom Res* 2009;66(5):445-54. doi:  
6  
7 10.1016/j.jpsychores.2008.12.007 [published Online First: 2009/04/22]  
8  
9 44. Christian LM, Glaser R, Porter K, et al. Poorer self-rated health is associated with elevated  
10 inflammatory markers among older adults. *Psychoneuroendocrinology* 2011;36(10):1495-504.  
11 doi: 10.1016/j.psyneuen.2011.04.003 [published Online First: 2011/05/24]  
12 45. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive  
13 minimal clinically important differences on the Functional Assessment of Cancer Therapy  
14 (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;24(6):547-61. [published  
15 Online First: 2003/01/29]  
16 46. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general  
17 United States population. *Cancer* 2002;94(2):528-38. doi: 10.1002/cncr.10245 [published  
18 Online First: 2002/03/20]  
19 47. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. *Arch*  
20 *Intern Med* 2000;160(4):526-34. [published Online First: 2000/03/01]  
21 48. Hasson D, Arnetz BB, Theorell T, et al. Predictors of self-rated health: a 12-month prospective  
22 study of IT and media workers. *Popul Health Metr* 2006;4:8. doi: 10.1186/1478-7954-4-8  
23 [published Online First: 2006/08/02]  
24 49. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors  
25 relating to fatigue in men and women. *Med Care* 1999;37(10):1078-83. [published Online  
26 First: 1999/10/19]  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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 entraînent 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

Annexes

## 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

## Annexes

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.

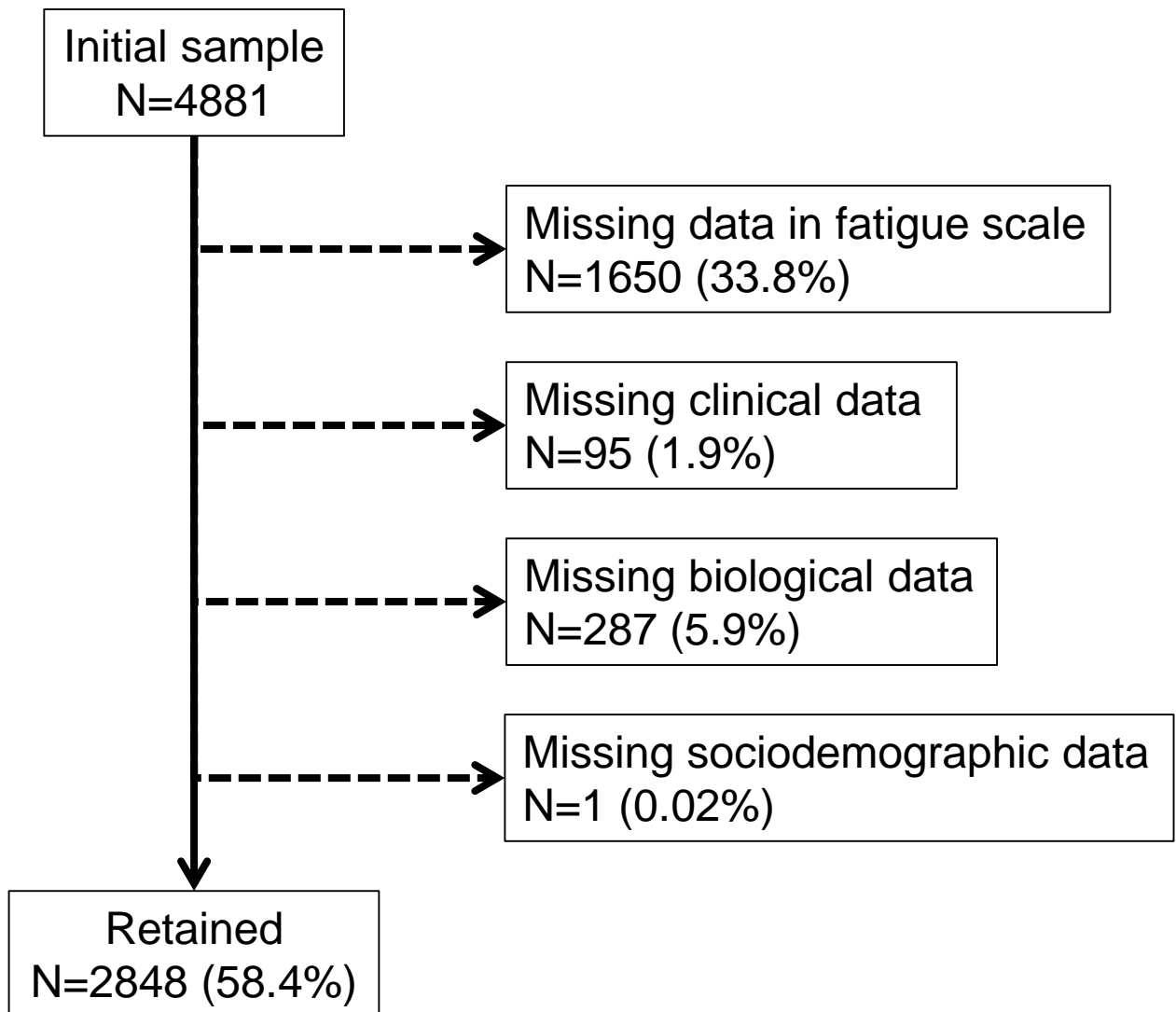
0-7	Pas d'insomnie
8-14	Insomnie légère
15-21	Insomnie modérée
22-28	Insomnie sévère

## Référence

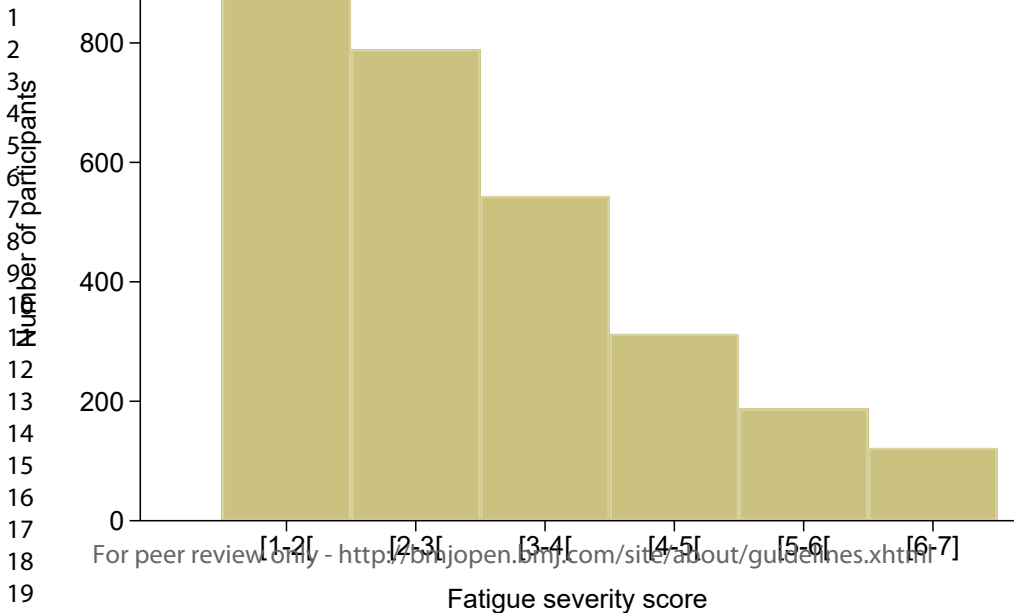
Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001; 2 : 297-307.



## 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 <sup>2</sup> )	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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**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  $\geq 5$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

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

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average  $\pm$  standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average  $\pm$  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		p-value	Multivariable model 1		Multivariable model 2	
	No fatigue	Fatigue		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							
2							
3	1-3/day	1603 (64.9)	189 (62.8)	-		-	
4	4-6/day	546 (22.1)	62 (20.6)	-		-	
5	7+/day	82 (3.3)	10 (3.3)	-		-	
6	Self-rated health			<0.001			
7	Very good	656 (25.9)	23 (7.4)		1 (ref)	1 (ref)	
8	Good	1505 (59.3)	112 (36.1)		1.61 (0.98 - 2.64)	0.062	1.58 (0.96 - 2.60)
9	Average	358 (14.1)	144 (46.5)		5.80 (3.40 - 9.87)	<0.001	5.65 (3.34 - 9.58)
10	Bad + Very bad	19 (0.8)	31 (10.0)		17.7 (7.32 - 42.6)	<0.001	17.2 (7.16 - 41.1)
11							<0.001
12	Cardiovascular disease			0.617			
13	No	2322 (91.5)	281 (90.7)		-	-	
14	Yes	216 (8.5)	29 (9.4)		-	-	
15	Diabetes			0.006			
16	No	2343 (92.5)	273 (88.1)		1 (ref)	1 (ref)	
17	Yes	189 (7.5)	37 (11.9)		0.99 (0.58 - 1.70)	0.975	0.99 (0.58 - 1.69)
18							0.979
19	Depression (CES-D)			<0.001			
20	No	2260 (91.8)	170 (57.4)		1 (ref)	1 (ref)	
21	Yes	203 (8.2)	126 (42.6)		3.31 (2.28 - 4.79)	<0.001	3.34 (2.31 - 4.83)
22							<0.001
23	Anemia			0.325			
24	No	2444 (96.3)	295 (95.2)		1 (ref)	-	
25	Yes	94 (3.7)	15 (4.8)		1.24 (0.60 - 2.59)	0.557	-
26	Ferritin categories			0.971			
27	>50	2294 (90.4)	280 (90.3)		-	-	
28	Normal + low	244 (9.6)	30 (9.7)		-	-	
29	TSH categories			0.842			
30	High > 4.22	223 (8.8)	30 (9.7)		1.50 (0.92 - 2.44)	0.105	-
31	Normal 0.27-4.22	2294 (90.4)	277 (89.4)		1 (ref)	-	-
32	Low < 0.27	21 (0.8)	3 (1.0)		0.63 (0.13 - 3.11)	0.566	-
33	Free T4 categories			0.636			
34	High > 22	58 (2.3)	6 (1.9)		-	-	
35	Normal 12-22	2419 (95.3)	294 (94.8)		-	-	
36	Low < 12	61 (2.4)	10 (3.2)		-	-	
37	Anti-hypertensive			0.461			
38	No	1755 (69.2)	208 (67.1)		-	-	
39							
40							
41							
42							
43							
44							
45							
46							

1								
2								
3	Yes	783 (30.9)	102 (32.9)		-		-	
4	Anti-histaminics			0.156				
5	No	2481 (97.8)	299 (96.5)		1 (ref)		-	
6	Yes	57 (2.3)	11 (3.6)		1.06 (0.47 - 2.42)	0.882	-	
7	Antidepressants			<0.001				
8	No	2330 (91.8)	240 (77.4)		1 (ref)		1 (ref)	
9	Yes	208 (8.2)	70 (22.6)		1.48 (0.97 - 2.25)	0.070	1.46 (0.96 - 2.21)	0.076
10	Hypnotics			0.004				
11	No	2439 (96.1)	287 (92.6)		1 (ref)		1 (ref)	
12	Yes	99 (3.9)	23 (7.4)		0.61 (0.31 - 1.23)	0.167	0.63 (0.31 - 1.26)	0.190
13								
14								

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  $\geq 4$  of the fatigue severity scale, while model 2 included only the variables significantly ( $p < 0.05$ ) associated with fatigue using the threshold of  $\geq 5$  of the fatigue severity scale.

**Supplemental table 5:** Multivariable analysis of the categorical determinants of fatigue (defined as a fatigue severity score  $\geq 4$ ) 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027070.R3
Article Type:	Research
Date Submitted by the Author:	23-Jul-2019
Complete List of Authors:	Galland, Coralie; Centre Hospitalier Universitaire Vaudois, Médecine Marques-Vidal, Pedro; Lausanne University Hospital, Department of Internal Medicine Vollenweider, Peter; Lausanne University Hospital, Internal Medicine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	General practice / Family practice
Keywords:	fatigue, prevalence, fatigue severity scale, EPIDEMIOLOGY

SCHOLARONE™  
Manuscripts

1  
2  
3 **Prevalence and factors associated with fatigue in the Lausanne**  
4 **middle-aged population: A population based cross-sectional**  
5 **survey**  
6

7 Coralie Galland-Decker, Pedro Marques-Vidal and Peter Vollenweider  
8  
9

10 Department of Medicine, Internal Medicine, Lausanne university hospital, Lausanne,  
11  
12 Switzerland  
13  
14

15 **Authors' emails:**

16 Coralie Galland-Decker: [Coralie.Galland@chuv.ch](mailto:Coralie.Galland@chuv.ch)

17 Pedro Marques-Vidal: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)

18 Peter Vollenweider: [Peter.Vollenweider@chuv.ch](mailto:Peter.Vollenweider@chuv.ch)  
19  
20  
21  
22

23 **Address for correspondence and reprints**

24 Pedro Marques-Vidal

25 Office BH10-642.

26 Department of Medicine, Internal Medicine.

27 Lausanne university hospital.

28 Rue du Bugnon 46, 1011, Lausanne, Switzerland.

29 Phone: +41 21 314 09 34

30 Email: [Pedro-Manuel.Marques-Vidal@chuv.ch](mailto:Pedro-Manuel.Marques-Vidal@chuv.ch)  
31  
32  
33  
34  
35  
36  
37

38 **Word count:** 4647  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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  $\geq 4$  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.



1  
2  
3 **Keywords:** fatigue; prevalence; epidemiology; Fatigue severity scale  
4  
5

6 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
7

- 8 - This study assessed the prevalence and factors associated with fatigue in a general  
9 population setting.  
10  
11 - A large panel of associated with fatigue was evaluated.  
12  
13 - A list of the most frequent determinants was established, facilitating etiological  
14 search in clinical practice  
15  
16 - The study was limited to subjects aged 45 to 86, so results do not apply to younger  
17 or older groups.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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”.<sup>1</sup>

Fatigue varies in duration and intensity and reduces the ability to perform usual daily activities.

<sup>1</sup> Indeed, fatigue is a common symptom with prevalence rates varying between 4 and 45%.<sup>2-</sup>

<sup>4</sup> This ten-fold range in prevalence rates is likely due to the different settings (i.e. general practice<sup>5</sup> or workers<sup>6</sup>) or the different methods used to assess fatigue.<sup>7</sup>

In healthy subjects, tiredness or sleepiness are a natural occurrence after physical or mental efforts, and are usually relieved by rest.<sup>8-9</sup> While fatigue is defined as extreme and persistent tiredness, weakness or exhaustion, of mental and/or physical origin<sup>7</sup> that is not relieved by rest. Fatigue is defined in duration as recent (<1 month) prolonged (1 to 6 months) and chronic (>6 months)<sup>10</sup>. 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)<sup>11</sup> or as idiopathic (absence of other symptoms).

Fatigue is one of the most common complaints reported in primary care<sup>12</sup> and is associated with a decreased quality of life and increased morbidity and mortality in the general population.<sup>13</sup> 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.<sup>10</sup> 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.<sup>14</sup> Fatigue has also been associated with female sex,<sup>8-15</sup> older age<sup>16-17</sup> and lower socioeconomic status,<sup>16-17</sup> although the association with the last two determinants were not found in some studies.<sup>8-18</sup> Importantly, most studies on fatigue have been conducted in selected populations such as workers<sup>6</sup> or general practice attendees.<sup>2-5-18</sup> To our knowledge, only two studies have assessed the prevalence of fatigue in the general population<sup>8-19</sup> and only a few have explored the

1  
2  
3 determinants of fatigue in the general population.<sup>13 15-17 20 21</sup> Furthermore, most studies focused  
4 on socio-economic and disease determinants of fatigue, while information regarding the  
5 biological determinants (i.e. anemia or thyroid pathology)<sup>13</sup> or the medications associated with  
6 fatigue is scarce. Moreover, to date, little is known about the prevalence of fatigue and its  
7 determinants in Switzerland.  
8  
9  
10  
11  
12

13  
14 Hence, this study aimed to examine the prevalence and the factors associated with  
15 fatigue in a population-based sample from the city of Lausanne, Switzerland.  
16  
17

## 18 19 **POPULATION AND METHODS**

### 20 21 **Study population**

22  
23 The CoLaus study is a population-based cohort exploring biological, genetic, and  
24 environmental determinants of cardiovascular diseases. Detailed descriptions of the study  
25 design have been reported elsewhere.<sup>22</sup> Briefly, a non-stratified random representative  
26 sample of the population of Lausanne was recruited between 2003 and 2006 using the  
27 following inclusion criteria: i) aged between 35 and 75 years and ii) willingness to participate.  
28 The first follow-up was performed between April 2009 and September 2012 and the second  
29 follow-up between May 2014 and April 2017, 10.9 years on average after the baseline study.  
30 At both baseline and subsequent follow-ups, participants were invited to attend a clinical  
31 examination at the Lausanne university hospital. Participants received a paper questionnaire  
32 at home, which they filled prior to the clinical examination. During the clinical examination, a  
33 second questionnaire regarding personal and family history of cardiovascular disease and  
34 cardiovascular risk factors was applied. For more details, please consult [www.colaus-psycolaus.ch](http://www.colaus-psycolaus.ch).  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50

51  
52 As fatigue was only assessed in the second follow-up, data from the second follow-up,  
53 which included 4881 of the initial 6773 participants recruited at baseline, was used. At the  
54 second follow-up, participants were aged 45-86 years.  
55  
56  
57  
58  
59  
60

## Fatigue scale

Fatigue severity during the previous week was assessed by the 9 items Fatigue Severity Scale (FSS).<sup>9</sup> The FSS is one of the most commonly used fatigue questionnaires. It had been validated in a healthy population setting in German-speaking Switzerland<sup>23</sup>, Portugal<sup>24</sup> and Norway<sup>19</sup>. It is a simple, time-saving, self-administrated questionnaire allowing its use in large epidemiological studies and has a high test-retest reliability.<sup>7</sup> 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  $\geq 4$  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.<sup>9</sup> 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).<sup>25</sup> 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

1  
2  
3 **Annex 4** in English. Clinically significant insomnia was defined as an ISI score  $\geq 15$  (moderate  
4 to severe intensity).<sup>25</sup>  
5  
6  
7

8 Depression was assessed with the CES-D <sup>26</sup>, a 20 item self-report instrument,  
9 developed for research in the general population, that is used to assess the severity of  
10 depressive symptoms over the past week on a 4-point scale. It was translated into French by  
11 Fuhrer and Rouillon.<sup>27</sup> It has been used in other recent epidemiological studies assessing the  
12 link between depression and cardiovascular risk factors <sup>28</sup>. The questionnaire is composed of  
13 20 questions; responses are graded from 0 to 3, where 0 indicates rarely or never (less than  
14 one day) and 4 most or all of the time (5-7 days per week). The final score is the sum of the  
15 20 responses (possible range is 0-60), and a score  $\geq 16$  is considered as a risk for depression.  
16  
17  
18  
19  
20  
21  
22  
23  
24

25 Self-rated health was assessed by a single question where participants had to rate  
26 their current health status from five categories ranging from “very bad” to “very good”. As the  
27 number of participants rating their health as “very bad” was very small, they were grouped with  
28 the participants who rated their health as “bad”.  
29  
30  
31  
32  
33

34 Body weight and height were measured with participants standing without shoes in  
35 light indoor clothing. Weight was measured in kilograms to the nearest 0.1 kg using a Seca™  
36 scale (Seca, Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca™  
37 height gauge (Seca, Hamburg, Germany). Body mass index (BMI) was defined as  
38 weight/height<sup>2</sup> and categorized as underweight (BMI < 18.5 kg/m<sup>2</sup>), normal (18.5 ≤ BMI < 25  
39 kg/m<sup>2</sup>); overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>) and obese (BMI ≥ 30 kg/m<sup>2</sup>).  
40  
41  
42  
43  
44  
45  
46

47 Grip strength was assessed using the Baseline® Hydraulic Hand Dynamometer  
48 (Fabrication Enterprises Inc., Elmsford, NY, USA) with the subject seated, shoulders adducted  
49 and neutrally rotated, elbow flexed at 90°, forearm in neutral position and wrist between 0 and  
50 30° of dorsiflexion. Three measurements were performed consecutively with the right hand  
51 and the highest value (expressed in kg) was included in the analyses.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Caffeinated drink consumption was assessed by the question “How many cups or cans  
4 of drinks containing caffeine (coffee, tea, coke or similar) do you drink per day?” with possible  
5 answers “None”, “1-3”, “4-6” and “7 or more”.  
6  
7  
8

9  
10 Participants were asked to report all medications (prescribed or bought over the  
11 counter) they took during the last 6 months. Medications were coded using the Anatomical,  
12 Therapeutic Chemical (ATC) classification of the world health organization  
13 ([www.whooc.no/atc\\_ddd\\_index/](http://www.whooc.no/atc_ddd_index/)). Antihistamics were defined as any ATC code beginning with  
14 “R06”; antidepressants were defined as an ATC code beginning with “N05BD” or “N06AA” or  
15 “N06AB” or “N06AF” or “N06AG” or “N06AX” or “N06CA”; hypnotics were defined as any ATC  
16 code beginning with “N05C”. Antihypertensive drugs were defined by asking the participants  
17 if they were taking drugs for hypertension.  
18  
19  
20  
21  
22  
23  
24  
25

26  
27 Diabetes was defined by a fasting plasma glucose  $\geq 7$  mmol/L and/or the presence of  
28 an antidiabetic drug treatment (oral or insulin). Personal history of cardio vascular disease was  
29 assessed by asking the participant if he/she had sustained a coronary event (myocardial  
30 infarction or angina pectoris) or a stroke.  
31  
32  
33  
34  
35

36 Biological assays were performed by the CHUV Clinical Laboratory on fresh blood  
37 samples within 2 hours of blood collection, and additional aliquots were stored at  $-80^{\circ}\text{C}$ . All  
38 measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland).  
39 The following analytical procedures (with maximum inter and intra-batch CVs) were used: high  
40 sensitive CRP by immunoassay and latex HS (4.6% – 1.3%); transferrin by immunoassay  
41 (1.8% – 1.0%); glucose by glucose dehydrogenase (2.1% – 1.0%). Ferritin was assessed by  
42 immunoturbidimetric method (Tina-quant 4<sup>th</sup> generation, Roche Diagnostics, Switzerland) with  
43 a maximum intra-assay CV of 7.2% and a maximum inter-assay CV of 9.9%. Thyroid  
44 stimulating hormone (TSH) and free  $T_4$  were assessed by chemiluminescence (ECLIA) on a  
45 Cobas e602 device (Roche diagnostics GmbH, Mannheim, Germany) with intra-batch CVs  
46 ranging between 1.1% and 3.0% for TSH and between 2.7% and 5% for free  $T_4$ .  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 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](http://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.

1  
2  
3 Sensitivity analyses were conducted using a FSS threshold of 5. Further, as the  
4 number of excluded participants was high, other sensitivity analyses were conducted by  
5 creating a propensity score for being excluded<sup>29</sup>. The propensity score was computed using  
6 logistic regression, with exclusion (yes/no) as dependent variable and all variables significantly  
7 associated with exclusion as independent variables. A probability of exclusion was computed  
8 for each participant, and the inverse of the probability was used for weighting.  
9  
10  
11  
12  
13  
14

15  
16 Statistical significance was assessed for a two-sided test with  $p < 0.05$ .  
17  
18

## 19 **RESULTS**

### 20 **Study population**

21  
22 Of the 4881 participants in the second follow-up, 2848 (58.4%) were retained for  
23 analysis. The reasons for exclusion are summarized in **supplemental figure 1**; the most  
24 frequent reason was lack of data regarding fatigue. The comparison between included and  
25 excluded participants is provided in **supplemental table 1** and the results of the multivariable  
26 analysis are provided in **supplemental table 2**. Excluded participants were more frequently  
27 women, were older, had a lower educational level, were more frequently never or current  
28 smokers, had more comorbidities (cardiovascular diseases, diabetes, anaemia, and  
29 hypertension) and rated their health worse.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

### 44 **Prevalence and factors associated with fatigue**

45  
46 The overall prevalence of fatigue as defined by a FSS  $\geq 4$  was 21.9% (95% CI: 20.4%  
47 – 23.4%) and was higher in women 23.4% (21.3% - 25.7%) than in men 20.1% (18.0% -  
48 22.3%),  $p = 0.031$ . The distribution of the FSS  $\geq 5$  (prevalence of fatigue 10.9%) is provided in  
49 **supplemental figure 2**; the number of participants with fatigue decreased when the levels of  
50 FSS increased.  
51  
52  
53  
54  
55

56  
57 The analysis of the factors associated with fatigue as defined by a FSS  $\geq 4$  is provided  
58 in **Tables 1 and 2**.  
59  
60



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

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

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average  $\pm$  standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average  $\pm$  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  $\geq 4$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate		p-value	Multivariable	
	No fatigue	Fatigue		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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

1  
2  
3 (2.38-4.46)], anemia [1.70 (1.00-2.89)] and low self-rated health status (p-value for trend  
4 <0.001) were positively associated, while older age (p-value for trend 0.002) was negatively  
5 associated with fatigue. Conversely, no association was found for diabetes, TSH levels, anti-  
6 histaminics or hypnotics (**Table 2**).

### 11 **Sensitivity analyses**

12  
13  
14 The overall prevalence of fatigue as defined by a FSS  $\geq 5$  was 10.9% (95% CI: 9.7% –  
15 12.1%) and was higher in women 12.3% (10.7% - 14.0%) than in men 9.3% (7.8% - 11.1%),  
16 p=0.011. The results of the sensitivity analyses using a FSS threshold of  $\geq 5$  are provided in  
17 **supplemental tables 3 and 4**. Overall, the results were comparable with those using a  
18 threshold of  $\geq 4$ : gender, insomnia categories (p-value for trend <0.001), and low self-rated  
19 health status (p-value for trend <0.001) were positively associated with fatigue. Conversely,  
20 no association was found for age, obesity, diabetes, TSH levels, antihistaminics,  
21 antidepressives or hypnotics (**supplemental table 4**).

22  
23  
24 Sensitivity analysis using inverse probability weighting by the propensity score led to  
25 similar findings, except that anemia and antidepressants were no longer associated with  
26 fatigue, while a positive association was found between low TSH levels and fatigue  
27 (**Supplemental table 5**).

### 31 **DISCUSSION**

32  
33  
34 To our knowledge, this is one of the few studies assessing the prevalence and the  
35 factors associated with fatigue in a general population setting, and the first study conducted  
36 in Switzerland. Using a FSS cut-off  $\geq 4$ , our results indicate that one out of five people aged  
37 between 45 and 86 years presents with fatigue, and that obesity, insomnia, depression and  
38 decreasing self-rated health status were positively associated with fatigue; while older age  
39 was negatively associated with fatigue.

### Prevalence of fatigue

Using the cut-off of  $\geq 4$ , fatigue was present in one out of five participants (22.1%), a finding in agreement with the study by Loge et al.<sup>8</sup>, which reported a prevalence of 22% among 2323 participants using the Chalder fatigue scale. Conversely, the cross-sectional study by Lerdal et al.<sup>19</sup>, 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  $\geq 4$  and  $\geq 5$  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,<sup>2</sup> whereas a study conducted in the Dutch working population reported a prevalence of fatigue of 22% using other fatigue measures.<sup>6</sup> 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<sup>8 15</sup> but not in others.<sup>18</sup> In a Swedish study conducted in 2014, Engberg et al.<sup>16</sup> 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.

1  
2  
3 Younger people reported fatigue more frequently than elderly, a finding in agreement  
4 with a Swedish study conducted in 2014.<sup>16</sup> Similarly, a previous study found that older  
5 subjects complain less of sleepiness.<sup>30</sup> Still, this association was no longer statistically  
6 significant when the cut off of  $\geq 5$  was applied to define fatigue, suggesting that young subjects  
7 tend to present with borderline fatigue as suggested previously<sup>19</sup>. Conversely, earlier studies  
8 (1990-2000) found a positive association between age and fatigue.<sup>8 17 21</sup> A possible  
9 explanation for this difference is that older people might have a better quality of life nowadays  
10 and are less depressed. Although there is little information regarding trends in quality of life  
11 among Swiss elderly, the VLV study<sup>31</sup> concluded that quality of life among Swiss elderly  
12 increased in the last 30 years<sup>32</sup>. Indeed, in our study, the lowest prevalence of fatigue was  
13 reported by participants aged 64-74 years, which are the “young” retired with few  
14 comorbidities. Similarly, the prevalence of depression was lower in elderly than in younger  
15 participants (8.1% and 10.2% in the 65-74 and the 75+ years, respectively, vs. 15.1% and  
16 12.5% in the 45-54 and 55-64 years, respectively,  $p$ -value $<0.001$ ).

17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Obese subjects had a higher prevalence of fatigue defined by a FSS  $\geq 4$ . This finding  
is in agreement with studies conducted in the USA<sup>33</sup> and in the UK.<sup>13</sup> Still, this association  
was no longer statistically significant when the cut off of  $\geq 5$  was applied to define fatigue,  
suggesting that obese subjects tend to present with borderline fatigue as suggested previously<sup>19</sup>.  
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.<sup>34</sup> 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,<sup>35</sup> which would lead to higher fatigue,<sup>36</sup> 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.

1  
2  
3 Fatigue is a core symptom of insomnia<sup>34</sup> and a Norwegian study conducted in 2014 showed  
4 that reducing insomnia severity led to a concomitant reduction in fatigue.<sup>37</sup> Interestingly, many  
5 subjects with sleep complaints do not consult for this issue,<sup>38</sup> which might lead to an  
6 underestimation of its prevalence. Overall, our results suggest that insomnia is an important  
7 and underestimated factor of fatigue.  
8  
9  
10  
11  
12

13  
14 Both depression and antidepressant medication were independently and positively  
15 associated with fatigue. The association between depression and fatigue has been  
16 repeatedly reported,<sup>13 39-41</sup> and the same applies for antidepressant medication.<sup>3</sup> Our  
17 results confirm the known association between depression and fatigue, and suggest that  
18 antidepressant treatment might not systematically relieve fatigue among depressive  
19 subjects. Furthermore, fatigue is a common side effect of antidepressant therapy and a  
20 symptom of depression, making the identification of the cause of fatigue difficult with a  
21 possibility of reverse causality (fatigue leading to depression and vice versa). We used a  
22 one-dimensional tool to evaluate fatigue (FSS); hence, we cannot distinguish between  
23 physical and mental fatigue. There is considerable overlap in phenomenology of fatigue  
24 and depression or anxiety but there are some important differences. People with fatigue  
25 without psychiatric symptoms tend to attribute their symptoms to external causes.  
26 Conversely, most depressed people experience self-blame or lowered self-esteem<sup>42</sup>.  
27 Further, fatigue and depression commonly appear together. A study conducted in 2009 by  
28 Harvey et al.<sup>43</sup>, showed that 7% of fatigued persons have no psychiatric symptoms, but  
29 remained at increased risk of later psychiatric disorder independently of the severity of  
30 fatigue.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

50 A strong association was found between poor self-rated health and fatigue, a finding  
51 also reported elsewhere.<sup>6 16</sup> Low self-rated health has been associated with increased levels  
52 of inflammatory markers such as interleukin 6 and CRP,<sup>44</sup> which in turn could trigger fatigue.  
53 Conversely, increased fatigue might lead to a lower rating of health status.  
54  
55  
56  
57  
58  
59  
60

### **Biological factors associated with fatigue**

Participants with anemia had a higher likelihood of reporting fatigue. This finding is in agreement with the literature,<sup>45 46</sup> although no association between fatigue and low haemoglobin levels was found in a UK study.<sup>13</sup> 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.<sup>10</sup> 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.<sup>10</sup> Basu et al. found no association between TSH categories and fatigue<sup>13</sup> and Canaris et al<sup>47</sup> 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.<sup>22</sup> 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



1  
2  
3 work environment) could improve sleep quality, increase self-rated health<sup>48</sup> and consequently  
4  
5 reduce fatigue.  
6  
7  
8  
9

### 10 **Strengths and limitations**

11  
12 This study has several strengths. Firstly, it is one of the few studies assessing the  
13 prevalence and the factors associated with fatigue in a population-based sample, which is of  
14 interest for public health. Secondly, it explored a large panel of possible factors associated  
15 with fatigue, thus allowing the identification of factors significantly and independently  
16 associated with fatigue.  
17  
18  
19  
20  
21  
22

23 This study has also several limitations. Firstly, its cross sectional setting precludes the  
24 identification of the causes of fatigue, as reverse causality is possible (i.e. fatigue leading to  
25 depression and vice-versa).<sup>3</sup> All participants of the CoLaus study are currently being re-  
26 contacted and re-examined, so a prospective analysis of the causes of fatigue will be feasible  
27 within two years. Secondly, there is no gold standard for the evaluation of fatigue and no  
28 official definition of fatigue. Hence, results might vary according to the scale applied or how  
29 participants interpret the term "fatigue". In this study, we chose to use a scale that was  
30 previously applied by other authors to facilitate comparisons. Thirdly, only the German version  
31 of the FSS has been validated in Switzerland; the French version used in this study has not  
32 yet been validated. Hence, it is possible that the true prevalence levels of fatigue might be  
33 under- or over-estimated, or that some items of the questionnaire might not be informative.  
34  
35 Still, the Cronbach's alpha for the questionnaire was 0.918, suggesting an excellent internal  
36 consistency. Furthermore, our results provide a first estimation of the prevalence of fatigue in  
37 the Swiss French-speaking general population, which could serve as a reference for further  
38 studies. Fourthly a sizable fraction of the sample was excluded, both between the baseline  
39 and the second follow-up, and within the current study, which might limit the generalizability  
40 of the findings. For instance, excluded participants were more frequently women; as women  
41 reported more frequently fatigue, this might lead to an underestimation of prevalence rates or  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 a decrease in the strength of the associations. Still, an analysis using a propensity score  
4 weighting for the probability of being excluded led to similar findings. Conversely, it was not  
5 possible to assess the reasons why participants did not complete the questionnaire. Fifthly,  
6 no information was available regarding shift work or the presence of very young children. Still,  
7 as a sizable fraction (almost 70%) of the sample was aged over 55 and over 36% of the sample  
8 was aged over 64, it is likely that the number of participants either on shift work or with very  
9 young children would be small. Sixthly, the FSS explored fatigue during the previous week  
10 while the ISI score explored the sleep during the previous month. Hence, it is possible that the  
11 time association between the two variables might not be optimal. Still, as the FSS lies within  
12 the period encompassed by the ISI, we believe that the associations obtained are clinically  
13 relevant. Seventhly, the study is limited to the population of aged 45 to 86, and its  
14 generalizability remains to be assessed. For instance, no information was collected regarding  
15 other confounders among younger subjects, where prevalence of fatigue might be higher due  
16 to parental and professional duties.<sup>49</sup> Finally, possible biases related to the self-reporting of  
17 fatigue could not be avoided, such as over- or under-estimation of symptoms or  
18 misunderstanding of what the term “fatigue” meant; still, this dilution bias would lead to a  
19 decrease in the strength of the associations, and it would be too restrictive in our opinion to  
20 provide a definition of the term “fatigue” to the participants, as different interpretations of the  
21 definition itself could also occur.

### 22 **Recommendations for future studies**

23  
24 Future studies on the prevalence of fatigue in the general population should focus on  
25 the following topics: 1) validate the questionnaires in the population of interest; 2) whenever  
26 possible, use a standardised questionnaire to allow comparison between studies.

27  
28 While some factors such as obesity<sup>13 33</sup>, depression<sup>13 39-41</sup> and antidepressor  
29 medications<sup>3</sup> were consistently associated with fatigue in our study and in the literature,  
30 controversial findings such as the association between fatigue and gender, age groups and  
31 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.

For peer review only

## **FUNDING**

The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401). The funding sources had no involvement in the study design, data collection, analysis and interpretation, writing of the report, or decision to submit the article for publication.

## **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-psycholaus.ch/> for information on how to submit an application for gaining access to CoLaus data.

## **ACKNOWLEDGEMENTS**

Not applicable.

## REFERENCES

1. Mota DD, Pimenta CA. Self-report instruments for fatigue assessment: a systematic review. *Res Theory Nurs Pract* 2006;20(1):49-78. [published Online First: 2006/03/21]
2. Pawlikowska T, Chalder T, Hirsch SR, et al. Population based study of fatigue and psychological distress. *BMJ* 1994;308(6931):763-6. [published Online First: 1994/03/19]
3. Guessous I, Favrat B, Cornuz J, et al. [Fatigue: review and systematic approach to potential causes]. *Rev Med Suisse* 2006;2(89):2725-31. [published Online First: 2007/02/16]
4. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. *J Epidemiol Community Health* 1992;46(2):92-7. [published Online First: 1992/04/01]
5. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. *Psychol Med* 1995;25(5):895-905. [published Online First: 1995/09/01]
6. Bultmann U, Kant I, Kasl SV, et al. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. *J Psychosom Res* 2002;52(6):445-52. [published Online First: 2002/06/19]
7. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;56(2):157-70. doi: 10.1016/S0022-3999(03)00371-4 [published Online First: 2004/03/16]
8. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;45(1):53-65. [published Online First: 1998/08/28]
9. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-3. [published Online First: 1989/10/01]
10. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006;174(6):765-7. doi: 10.1503/cmaj.1031153 [published Online First: 2006/03/15]
11. Reid S, Chalder T, Cleare A, et al. Chronic fatigue syndrome. *BMJ* 2000;320(7230):292-6. [published Online First: 2000/01/29]
12. Cullen W, Kearney Y, Bury G. Prevalence of fatigue in general practice. *Ir J Med Sci* 2002;171(1):10-2. [published Online First: 2002/05/08]

- 1  
2  
3 13. Basu N, Yang X, Luben RN, et al. Fatigue is associated with excess mortality in the general  
4  
5 population: results from the EPIC-Norfolk study. *BMC Med* 2016;14(1):122. doi:  
6  
7 10.1186/s12916-016-0662-y [published Online First: 2016/08/21]  
8
- 9 14. Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a  
10  
11 primary care practice. *Arch Intern Med* 1993;153(24):2759-65. [published Online First:  
12  
13 1993/12/27]  
14
- 15 15. Fieo RA, Mortensen EL, Lund R, et al. Assessing fatigue in late-midlife: increased scrutiny of the  
16  
17 Multiple Fatigue Inventory-20 for community-dwelling subjects. *Assessment* 2014;21(6):706-  
18  
19 12. doi: 10.1177/1073191114541143 [published Online First: 2014/07/06]  
20
- 21 16. Engberg I, Segerstedt J, Waller G, et al. Fatigue in the general population- associations to age,  
22  
23 sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern  
24  
25 Sweden MONICA study 2014. *BMC Public Health* 2017;17(1):654. doi: 10.1186/s12889-017-  
26  
27 4623-y [published Online First: 2017/08/16]  
28
- 29 17. Watt T, Groenvold M, Bjorner JB, et al. Fatigue in the Danish general population. Influence of  
30  
31 sociodemographic factors and disease. *J Epidemiol Community Health* 2000;54(11):827-33.  
32  
33 [published Online First: 2000/10/12]  
34
- 35 18. David A, Pelosi A, McDonald E, et al. Tired, weak, or in need of rest: fatigue among general  
36  
37 practice attenders. *BMJ* 1990;301(6762):1199-202. [published Online First: 1990/11/24]  
38
- 39 19. Lerdal A, Wahl A, Rustoen T, et al. Fatigue in the general population: a translation and test of the  
40  
41 psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J Public*  
42  
43 *Health* 2005;33(2):123-30. doi: 10.1080/14034940410028406 [published Online First:  
44  
45 2005/04/13]  
46
- 47 20. Boter H, Manty M, Hansen AM, et al. Self-reported fatigue and physical function in late mid-life. *J*  
48  
49 *Rehabil Med* 2014;46(7):684-90. doi: 10.2340/16501977-1814 [published Online First:  
50  
51 2014/05/14]  
52
- 53 21. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie* 2003;26(2):140-4. doi:  
54  
55 10.1159/000069834 [published Online First: 2003/05/29]  
56
- 57 22. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate  
58  
59 the epidemiology and genetic determinants of cardiovascular risk factors and metabolic  
60

- 1  
2  
3 syndrome. *BMC Cardiovasc Disord* 2008;8:6. doi: 10.1186/1471-2261-8-6 [published Online  
4 First: 2008/03/28]  
5  
6  
7 23. Valko PO, Bassetti CL, Bloch KE, et al. Validation of the fatigue severity scale in a Swiss cohort.  
8  
9 *Sleep* 2008;31(11):1601-7. [published Online First: 2008/11/19]  
10  
11 24. Laranjeira CA. Translation and adaptation of the fatigue severity scale for use in Portugal. *Appl*  
12  
13 *Nurs Res* 2012;25(3):212-7. doi: 10.1016/j.apnr.2010.11.001 [published Online First:  
14 2012/06/16]  
15  
16 25. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome  
17  
18 measure for insomnia research. *Sleep Med* 2001;2(4):297-307. [published Online First:  
19 2001/07/05]  
20  
21  
22 26. LS R. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population.  
23  
24 *Applied Psychological Measurement* 1977;1((3)):385-401.  
25  
26 27. FR RF. The French version of the CES-D (Center for Epidemiologic Studies-Depression Scale).  
27  
28 *European Psychiatry* 1989;4(3):163-66.  
29  
30 28. Hamieh N, Meneton P, Wiernik E, et al. Depression, treatable cardiovascular risk factors and  
31  
32 incident cardiac events in the Gazel cohort. *Int J Cardiol* 2018 doi:  
33 10.1016/j.ijcard.2018.10.013 [published Online First: 2018/10/12]  
34  
35 29. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding  
36  
37 in Observational Studies. *Multivariate Behav Res* 2011;46(3):399-424. doi:  
38 10.1080/00273171.2011.568786 [published Online First: 2011/08/06]  
39  
40  
41 30. Luca G, Haba Rubio J, Andries D, et al. Age and gender variations of sleep in subjects without  
42  
43 sleep disorders. *Ann Med* 2015;47(6):482-91. doi: 10.3109/07853890.2015.1074271  
44  
45 [published Online First: 2015/08/01]  
46  
47 31. Ludwig C, Cavalli S, Oris M. "Vivre/Leben/Vivere": An interdisciplinary survey addressing progress  
48  
49 and inequalities of aging over the past 30 years in Switzerland. *Arch Gerontol Geriatr*  
50  
51 2014;59(2):240-8. doi: 10.1016/j.archger.2014.04.004 [published Online First: 2014/05/24]  
52  
53 32. no authors listed. Qualité de vie des seniors en Suisse. In: Centre interfacultaire de gérontologie  
54  
55 et d'études des vulnérabilités, Pôle de Recherche National LIVES, eds. Geneva, Switzerland:  
56 University of Geneva, 2015:4.  
57  
58  
59  
60

- 1  
2  
3 33. Resnick HE, Carter EA, Aloia M, et al. Cross-sectional relationship of reported fatigue to obesity,  
4 diet, and physical activity: results from the third national health and nutrition examination  
5 survey. *J Clin Sleep Med* 2006;2(2):163-9. [published Online First: 2007/06/15]  
6  
7  
8  
9 34. Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population  
10 sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol*  
11 *Metab* 2005;90(8):4510-5. doi: 10.1210/jc.2005-0035 [published Online First: 2005/06/09]  
12  
13  
14 35. Marques-Vidal P, Bochud M, Bastardot F, et al. Association between inflammatory and obesity  
15 markers in a Swiss population-based sample (CoLaus Study). *Obes Facts* 2012;5(5):734-44.  
16 doi: 10.1159/000345045 [published Online First: 2012/10/31]  
17  
18  
19 36. Vgontzas AN, Bixler EO, Chrousos GP. Obesity-related sleepiness and fatigue: the role of the  
20 stress system and cytokines. *Ann N Y Acad Sci* 2006;1083:329-44. doi:  
21 10.1196/annals.1367.023 [published Online First: 2006/12/07]  
22  
23  
24 37. Kallestad H, Jacobsen HB, Landro NI, et al. The role of insomnia in the treatment of chronic  
25 fatigue. *J Psychosom Res* 2015;78(5):427-32. doi: 10.1016/j.jpsychores.2014.11.022  
26 [published Online First: 2014/12/17]  
27  
28  
29 38. Pires ML, Benedito-Silva AA, Mello MT, et al. Sleep habits and complaints of adults in the city of  
30 Sao Paulo, Brazil, in 1987 and 1995. *Braz J Med Biol Res* 2007;40(11):1505-15. [published  
31 Online First: 2007/10/16]  
32  
33  
34 39. Lawrie SM, Manders DN, Geddes JR, et al. A population-based incidence study of chronic fatigue.  
35 *Psychol Med* 1997;27(2):343-53. [published Online First: 1997/03/01]  
36  
37  
38 40. Wessely S, Chalder T, Hirsch S, et al. Psychological symptoms, somatic symptoms, and  
39 psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in  
40 the primary care setting. *Am J Psychiatry* 1996;153(8):1050-9. doi: 10.1176/ajp.153.8.1050  
41 [published Online First: 1996/08/01]  
42  
43  
44 41. Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic fatigue  
45 and psychiatric morbidity: results from a community survey in Great Britain. *Int Rev Psychiatry*  
46 2003;15(1-2):57-64. doi: 10.1080/0954026021000045958 [published Online First: 2003/05/15]  
47  
48  
49 42. Powell R, Dolan R, Wessely S. Attributions and self-esteem in depression and chronic fatigue  
50 syndromes. *J Psychosom Res* 1990;34(6):665-73. [published Online First: 1990/01/01]  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 43. Harvey SB, Wessely S, Kuh D, et al. The relationship between fatigue and psychiatric disorders:  
4  
5 evidence for the concept of neurasthenia. *J Psychosom Res* 2009;66(5):445-54. doi:  
6  
7 10.1016/j.jpsychores.2008.12.007 [published Online First: 2009/04/22]  
8  
9 44. Christian LM, Glaser R, Porter K, et al. Poorer self-rated health is associated with elevated  
10  
11 inflammatory markers among older adults. *Psychoneuroendocrinology* 2011;36(10):1495-504.  
12  
13 doi: 10.1016/j.psyneuen.2011.04.003 [published Online First: 2011/05/24]  
14  
15 45. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive  
16  
17 minimal clinically important differences on the Functional Assessment of Cancer Therapy  
18  
19 (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;24(6):547-61. [published  
20  
21 Online First: 2003/01/29]  
22  
23 46. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general  
24  
25 United States population. *Cancer* 2002;94(2):528-38. doi: 10.1002/cncr.10245 [published  
26  
27 Online First: 2002/03/20]  
28  
29 47. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. *Arch*  
30  
31 *Intern Med* 2000;160(4):526-34. [published Online First: 2000/03/01]  
32  
33 48. Hasson D, Arnetz BB, Theorell T, et al. Predictors of self-rated health: a 12-month prospective  
34  
35 study of IT and media workers. *Popul Health Metr* 2006;4:8. doi: 10.1186/1478-7954-4-8  
36  
37 [published Online First: 2006/08/02]  
38  
39 49. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors  
40  
41 relating to fatigue in men and women. *Med Care* 1999;37(10):1078-83. [published Online  
42  
43 First: 1999/10/19]  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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 entraînent 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

Annexes

## 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

## Annexes

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: \_\_\_\_\_

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

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

Very Satisfied				Very Dissatisfied
0	1	2	3	4

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

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

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

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

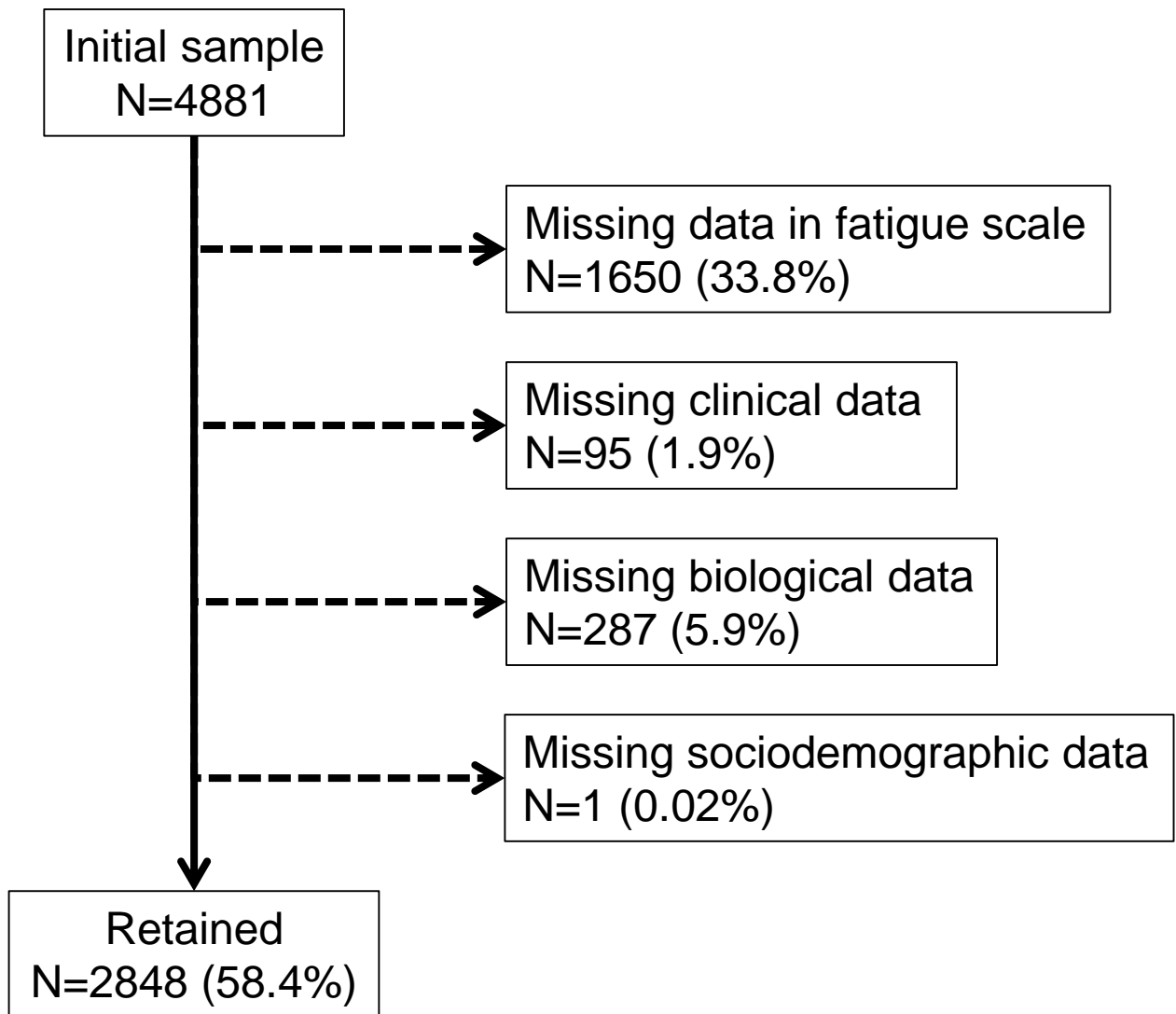
**Guidelines for Scoring/Interpretation:**

Add scores for all seven items (1a+1b+1c+ 2+3+4+5) = \_\_\_\_\_

Total score ranges from 0-28

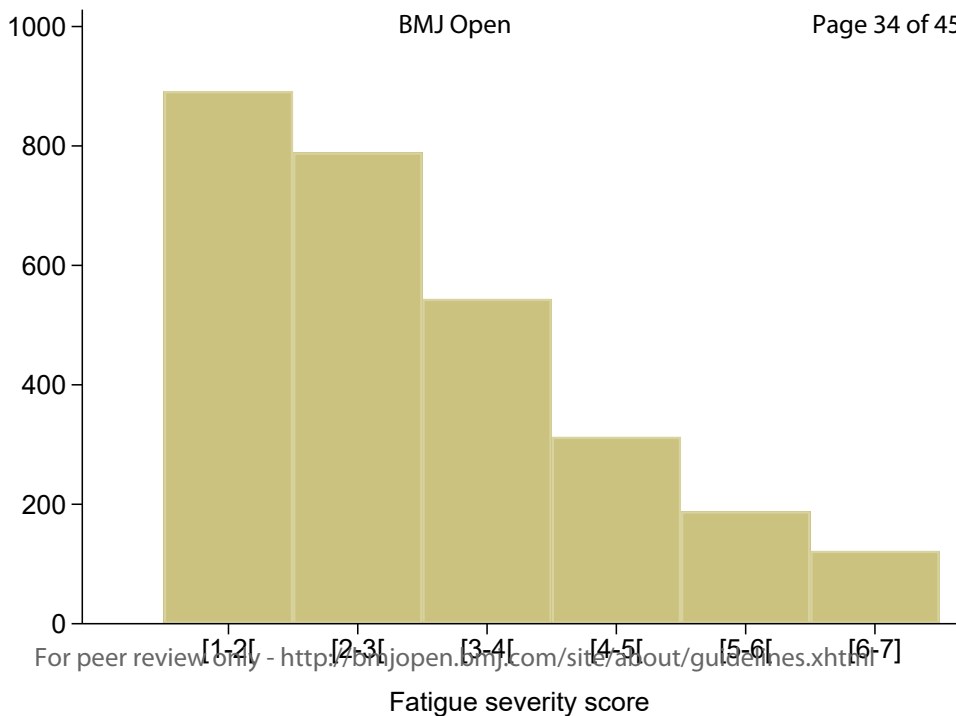
- 0-7 = No clinically significant insomnia
- 8-14 = Subthreshold insomnia
- 15-21 = Clinical insomnia (moderate severity)
- 22-28 = Clinical insomnia (severe)

## Supplemental figure 1: The reasons for exclusion



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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20





**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 <sup>2</sup> )	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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**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  $\geq 5$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

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

BMI, body mass index; TSH, thyroid stimulating hormone. Results are expressed as average  $\pm$  standard deviation or as median [interquartile range] for the bivariate analysis and as multivariable-adjusted average  $\pm$  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  $\geq 5$  in the CoLaus study, Lausanne, Switzerland, 2014-2017.

	Bivariate		p-value	Multivariable model 1		Multivariable model 2	
	No fatigue	Fatigue		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								
2								
3	1-3/day	1603 (64.9)	189 (62.8)		-		-	
4	4-6/day	546 (22.1)	62 (20.6)		-		-	
5	7+/day	82 (3.3)	10 (3.3)		-		-	
6	Self-rated health			<0.001				
7	Very good	656 (25.9)	23 (7.4)		1 (ref)		1 (ref)	
8	Good	1505 (59.3)	112 (36.1)		1.61 (0.98 - 2.64)	0.062	1.58 (0.96 - 2.60)	0.069
9	Average	358 (14.1)	144 (46.5)		5.80 (3.40 - 9.87)	<0.001	5.65 (3.34 - 9.58)	<0.001
10	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
11	Cardiovascular disease			0.617				
12	No	2322 (91.5)	281 (90.7)		-		-	
13	Yes	216 (8.5)	29 (9.4)		-		-	
14	Diabetes			0.006				
15	No	2343 (92.5)	273 (88.1)		1 (ref)		1 (ref)	
16	Yes	189 (7.5)	37 (11.9)		0.99 (0.58 - 1.70)	0.975	0.99 (0.58 - 1.69)	0.979
17	Depression (CES-D)			<0.001				
18	No	2260 (91.8)	170 (57.4)		1 (ref)		1 (ref)	
19	Yes	203 (8.2)	126 (42.6)		3.31 (2.28 - 4.79)	<0.001	3.34 (2.31 - 4.83)	<0.001
20	Anemia			0.325				
21	No	2444 (96.3)	295 (95.2)		1 (ref)		-	
22	Yes	94 (3.7)	15 (4.8)		1.24 (0.60 - 2.59)	0.557	-	
23	Ferritin categories			0.971				
24	>50	2294 (90.4)	280 (90.3)		-		-	
25	Normal + low	244 (9.6)	30 (9.7)		-		-	
26	TSH categories			0.842				
27	High > 4.22	223 (8.8)	30 (9.7)		1.50 (0.92 - 2.44)	0.105	-	
28	Normal 0.27-4.22	2294 (90.4)	277 (89.4)		1 (ref)		-	
29	Low < 0.27	21 (0.8)	3 (1.0)		0.63 (0.13 - 3.11)	0.566	-	
30	Free T4 categories			0.636				
31	High > 22	58 (2.3)	6 (1.9)		-		-	
32	Normal 12-22	2419 (95.3)	294 (94.8)		-		-	
33	Low < 12	61 (2.4)	10 (3.2)		-		-	
34	Anti-hypertensive			0.461				
35	No	1755 (69.2)	208 (67.1)		-		-	
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								

1							
2							
3	Yes	783 (30.9)	102 (32.9)	-	-	-	-
4	Anti-histaminics			0.156			
5	No	2481 (97.8)	299 (96.5)	1 (ref)		-	
6	Yes	57 (2.3)	11 (3.6)	1.06 (0.47 - 2.42)	0.882	-	
7	Antidepressants			<0.001			
8	No	2330 (91.8)	240 (77.4)	1 (ref)		1 (ref)	
9	Yes	208 (8.2)	70 (22.6)	1.48 (0.97 - 2.25)	0.070	1.46 (0.96 - 2.21)	0.076
10	Hypnotics			0.004			
11	No	2439 (96.1)	287 (92.6)	1 (ref)		1 (ref)	
12	Yes	99 (3.9)	23 (7.4)	0.61 (0.31 - 1.23)	0.167	0.63 (0.31 - 1.26)	0.190
13							
14							

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  $\geq 4$  of the fatigue severity scale, while model 2 included only the variables significantly ( $p < 0.05$ ) associated with fatigue using the threshold of  $\geq 5$  of the fatigue severity scale.



**Supplemental table 5:** Multivariable analysis of the categorical determinants of fatigue (defined as a fatigue severity score  $\geq 4$ ) 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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