Sleep disorders in COVID-19 patients: a monocentric prevalence study conducted on 337 patients

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Abstract

Introduction : Our study analysed the prevalence of sleep disorders (primarily insomnia and hypersomnia) in patients who tested positive for Covid 19, as well as the distribution of insomnia/hypersomnia in different subgroups of these patients (according to their age, gender, BMI, disease severity).
Materials and methods: This prospective, noninvasive, cross sectional study was conducted at the Emergency department, Respiratory Center, and Respiratory Intensive care Center of University Hospital Dubrava from December 2020. until March 2021. It included patients whose tested positive for Covid 19 and who reported at least one neurological symptom. Patients were examined, and interviewed face to face using a web – based structured questionnaire designed for the purposes of this study.
Results: Of the 337 participants, 109 (32,34%) reported one of two possible symptoms associated with sleep disorder, primarily difficulty sleeping/insomnia (dubbed „sleep disorder“) or sleepiness/hypersomnia. Of the 337 participants, 61 (18%) reported sleep disorder while 48 (14%) reported hypersomnia. There was no statistically significant difference in prevalence of sleep disorder between men and women ($\chi2$ = 0,113, p = 0,737). Hypersomnia was more prevalent in women ($\chi2$ = 8,125, p = 0,004). Patients who had sleep disorder had a lower median age by 5 years compared to patients who did not have a sleep disorder (z = 2,6, p = 0,009). Patients who had hypersomnia had a median of age lower for 9 years than patients who did not have hypersomnia (z = 4,3, p = <0,001). There was no significant difference in BMI between patients with and without hypersomnia (z = 0,157, p = 0,875). There was no association of hypersomnia with the presence of pneumonia ($\chi2$ = 0,000, p =1,000). In our study sleep disorder was associated with pneumonia ($\chi2$ = 6.4, p = 0.012). Of the patients with a sleep disorder, 59% of them reported dispnea, 78% had pneumonia and72% were hospitalized. Of the admitted patients, only two of them were transferred to the Respiratory intensive care and were treated using mechanical ventilation. In the patient group with hypersomnia, 46% of patients reported dispnea, 64% had pneumonia and 48% were hospitalized, of which one patient was hospitalized in Respiratory intensive care, and did not require treatmeant with mechanical ventilation.
Conclusion: Sleep disorders are prevalent in one form or the other in little over a third of patients with a Covid infection. Age, gender, and the presence of pneumonia are associated with different types of sleep disorders. More studies are needed to investigate the potential effect of sleep on the outcome of patients with COVID 19.

Keywords: Insomnia, Hypersomnia, COVID 19, Questionnaire, Prevalence

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Sažetak:

Poremećaji spavanja u COVID-19 pacijenata: monocentrično prevalencijskoistraživanje na 337 pacijenata

Uvod: Naša studija analizirala je prevalenciju poremećaja spavanja (prvenstveno nesanice i hipersomnije) kod pacijenata koji su bili pozitivni na Covid 19, kao i distribuciju nesanice/hipersomnije u različitim podskupinama ovih pacijenata (prema njihovoj dobi, spol, BMI, težina bolesti).

Materijali i metode: Ova prospektivna, neinvazivna, presječna studija provedena je u Objedinjenom hitnom prijemu Primarnog respiracijsko-intenzivističkog centra Kliničke bolnice Dubrava od prosinca 2020. do ožujka 2021. godine. U populaciji pacijenata koji su prijavili barem jedan neurološki simptom. Pacijenti su pregledani i intervjuirani licem u lice korištenjem strukturiranog upitnika.

Rezultati: Od 337 sudionika, 109 (32,34%) je prijavilo jedan od dva moguća simptoma povezana s poremećajem spavanja, prvenstveno poteškoće sa spavanjem/nesanicu (nazvan „poremećaj spavanja“) ili pospanost/hipersomniju. Od 337 sudionika, 61 (18%) je prijavilo poremećaj spavanja, dok je 48 (14%) prijavilo hipersomniju. Nije bilo statistički značajne razlike u prevalenciji poremećaja spavanja između muškaraca i žena ($\chi2 = 0,113$, $p = 0,737$). Hipersomnija je bila češća kod žena ($\chi2 = 8,125$, $p = 0,004$). Bolesnici koji su imali poremećaj spavanja imali su nižu srednju dob za 5 godina u odnosu na bolesnike koji nisu imali poremećaj spavanja ($z = 2,6$, $p = 0,009$). Bolesnici koji su imali hipersomniju imali su medijan dobi niži za 9 godina od pacijenata koji nisu imali hipersomniju ($z = 4,3$, $p = <0,001$). Nije bilo značajne razlike u BMI između bolesnika sa i bez hipersomnije ($z = 0,157$, $p = 0,875$). Nije bilo povezanosti hipersomnije s prisutnošću pneumonije ($\chi2 = 0,000$, $p = 1,000$). U našem istraživanju poremećaj spavanja bio je povezan s upalom pluća ($\chi2 = 6,4$, $p = 0,012$). Od pacijenata sa poremećaj spavanja, 59% njih prijavilo je dispneju, 78% imalo je upalu pluća, a 72% je hospitalizirano. Od primljenih pacijenata samo su dvoje prebačeni na Respiratornu intenzivnu njegu i liječeni su mehaničkom ventilacijom. U skupini bolesnika s hipersomnijom, 46% bolesnika prijavilo je dispneju, 64% je imalo upalu pluća, a 48% je hospitalizirano, od čega je jedan bolesnik hospitaliziran na intenzivnoj njezi dišnog sustava i nije zahtijevao liječenje mehaničkom ventilacijom.

Zaključak: Poremećaji spavanja prevladavaju u jednom ili drugom obliku u nešto više od trećine pacijenata s COVID infekcijom. Dob, spol i prisutnost upale pluća povezani su s različitim vrstama poremećaja spavanja. Potrebno je više studija kako bi se istražio potencijalni učinak sna na ishod pacijenata s COVID-19.

Ključne riječi: insomnija, hipersomnija, COVID 19, upitnik, prevalencija

Introduction

In December 2019. a global pandemic caused by a novel SARS CoV2 has started from China and spread uncontrollably across the globe. As of the end of October 2021, there have been 244,385,444 confirmed cases of COVID-19 around the world, including 4,961,489 deaths, reported by WHO (1). SARS CoV2 is a positive sense single-strand RNA virus, the seventh known coronavirus capable of infecting humans. Primarily recognized as a respiratory disease-causing virus, using ACE 2 receptors of the respiratory epithelial cell line to enter and replicate, the disease caused by SARS CoV2 was named COVID 19 by WHO in February 2020. Symptoms of COVID 19 vary from fever, cough, malaise, anorexia, diarrhea, difficulty breathing, and respiratory failure. Most of the patients develop a mild to moderate disease course, while those above 65 years, the ones living in a nursing home and bearing chronic comorbidities such as arterial hypertension, diabetes mellitus, BMI > 40, heart, pulmonary, liver, and kidney disease, develop more severe forms of COVID 19. (2,3) More and more studies report abundant neurological symptoms of COVID 19, with some revealing that 36% of patients with severe COVID 19 complain about neurological symptoms. (4) There have been proposals of potential neuroinvasive, and neurotoxic capabilities of SARS CoV2. (5,6,7,8,9). An unprecedented event in modern human history, the COVID 19 pandemic with its lockdowns, required self-isolation, the anxiety of „being in a susceptible group“, financial instabilities, has caused numerous new-onset sleep disorders in the general public, and COVID 19 positive patients. Besides the psychological effect of a global pandemic, studies are ruminating on the possible direct neuroinvasive, and neurotoxic effect of SARS CoV2 on sleep governing centers in COVID 19 positive patients (10). Reaching the hypothalamus, as well as the brainstem, SARS CoV2 by way of binding with ACE – 2 receptors has the poten-

tial to damage nuclei of the reticular activating system and areas of the brainstem regulating respiration. In this way it can cause new-onset changes in the sleep-wake cycle and new onset of sleep-related breathing disorders (10). Also, GABA interneurons of PVN with its expression of ACE – 2 receptors are a possible target by SARS CoV2 leading to changes in ultradian rhythm, increased propensity to anxiety, and sleep fragmentation (11). Sleep is a physiological state of the utmost value for energy metabolism, muscle restoration, tissue growth, cognitive function, and healthy governing of the immune system. The interaction of the immune system and sleep is extensively researched by now. Research has found that some of the cytokines such as TNF - α, and IL – 1β increase slow-wave sleep in dose dependant manner (12). When presented with acute infection or inflammation, cytokines such as IL – 1, IL – 6, TNF, and type I interferon using receptors on neurons, astrocytes, and microglia induct slow-wave sleep, increase sleep continuity, and consolidate sleep architecture. Also during normal sleep, the accumulation, and maturation of antigen presenting cells in lymphoid tissues enhances the diversity of T cells, promotes TH1 cell type immune, and helps control inflammation. In acute infection, cytokine-mediated sleep is used as means of conserving energy necessary for mounting an immune response to the pathogen (12,13,14). Meanwhile protracted and increased inflammation causes sleep fragmentation, increase in REM sleep, and loss of SWS (13). Their relationship being bidirectional studies show that sleep deprivation is associated with a shift towards TH 2 cell – type cytokine activity, prolonged, and increased secretion of IL – 6 during the day, and increased CRP, thus starting a vicious cycle of increased inflammation ↔ sleep disorder (12,13). It has been shown that short sleep duration also predicts pneumonia risk (<5 hours of sleep per night) (15).
With all of this in mind our study analyzed the prevalence of sleep disorders (insomnia/hypersomnia) in COVID 19 positive patients, and the distribution of sleep disorders in different groups of patients (according to age, gender, BMI, disease severity).

Materials and Methods

This was a prospective, noninvasive, cross-sectional study conducted at the Emergency Department, Respiratory Center, and Respiratory Intensive care Center of University Hospital Dubrava from December 2020. till March 2021. From March of 2020. University Hospital Dubrava was declared a medical referral center dedicated to the treatment of patients with a confirmed diagnosis of COVID 19. Therefore all patients treated in UH Dubrava were COVID 19 positive (confirmed with rRT – PCR analysis of throat and nasal swab specimens), and they all had gone through triage in ED of UH Dubrava. Afterwards, some of the patients were delegated to the respiratory center(hospital ward) or respiratory intensive care center (intensive care) for treatment. Inclusion criteria for this study, therefore, were the presence of at least one subjective neurological symptom, and the willingness to participate in the study. The ethics committee of UH Dubrava approved of this study, and all participants gave their verbal consent. The study was conducted following the Helsinki Declaration. Collecting of information was part of a standard history-taking interview and therefore improved our appreciation of variable symptoms of COVID 19, and helped us treat our patients better. Patients were examined, and face to face interviewed using a web-based structured questionnaire specifically designed for this study. The questionnaire collected demographic data such as age, gender, BMI, etc., subjective neurological symptoms (dichotomized answer yes/no), comorbidities (dichotomized answer yes/no), and presentation of the severity of clinical picture thru questions such as „need for hospitalization, need for intensive care, need for mechanical ventilation, presence of pneumonia, etc.“. To examine the prevalence of sleep disorders, and hypersomnia in different groups, and domains we quantified the number of positive answers for each patient, group, domain (men – women, patients younger/older, etc.) transformed them to median or percentage, and compared them to each other.
Data analysis was done using the statistical software IBM SPSS Statistics version 20, 2015. (New York, USA). We interpreted the results with P<0,05 as significant, and when comparing different groups used $\chi 2$ test and Mann – Whitney test.

Results

In our study, 337 patients reported at least one subjective neurological symptom and were eligible for participation. Of all patients 173 (51,33%) were men, and 164 (48,66%) were women. The median age of all participants was 64 (min-max;18-100). Median of BMI of all participants was 27,63 (min-max; 17,10 - 44,07). Of all 337 participants, 109 (32,34%) reported one of two possible symptoms associated with sleep disorder be it difficulty sleeping/insomnia (in further text dubbed „sleep disorder“) or sleepiness/hypersomnia. Of 337 participants 61 (18%) reported sleep disorder while 48 (14%) reported hypersomnia. There was no statistically significant difference in the prevalence of sleep disorder between men and women ($\chi 2$ = 0,113, p = 0,737) (Table 1.). But there was a statistically significant difference in hypersomnia prevalence between men and women ($\chi 2$ = 8,125, p = 0,004) (Table 2.). Of 164 women, 33 (20,1%) reported hypersomnia while of 173 men, 15 (8,7%) reported hypersomnia. We then divided patients into two groups. Those that had sleep disorder or hypersomnia and those that did not. We then proceeded to examine differences between those two different groups in age, BMI, presence of pneumonia, comorbidities, and disease severity. As seen in Table 3. patients who had sleep disorder had a lower median of age by 5 years than patients who did not have sleep disorder (z = 2,6, p = 0,009). Meaning that in our study patients who had sleep disorder were mainly of middle age, while patients who did not have sleep disorder

fell into the age category of aged individuals. There was also a statistically significant difference in BMI points between those who had and those who did not have a sleep disorder. Those who had sleep disorder had a median BMI score of 2 points greater than those who did not have a sleep disorder (z = 3,5, p = <0,001). This being statistically significant does not bear clinical significance being that both groups belong to an „Overweight" category according to BMI. We also found a statistically significant difference in age between patients with and without hypersomnia (Table 4.). Patients who had hypersomnia had a median of age lower for 9 years than patients who did not have hypersomnia (z = 4,3, p = <0,001). There was no significant difference in BMI between patients who had and those that did not have hypersomnia (z = 0,157, p = 0,875). In our study, there was no statistically significant association between hypersomnia and pneumonia, as seen in Table 5. The percentage of those who had hypersomnia was almost identical between those patients who had and those who did not have pneumonia in our study ($\chi 2$ = 0,000, p =1,000). When analyzing the association of sleep disorder and pneumonia we found statistical significance (Table 6.). In the group of subjects with pneumonia (n = 215), 48 (22%) of them had a sleep disorder, and in the group, without pneumonia (n = 122) 13 (11%) of them had a sleep disorder.
The share of sleep disorder in the group of patients with pneumonia is 2 times higher than the share of subjects with sleep disorder in the group of patients without pneumonia ($\chi 2$ = 6.4, p = 0.012). Table 7. shows a percentage of different comorbidities seen in patients with a sleep disorder. In patients reporting sleep disorder most prevalent comorbidities are : arterial hypertension (54,09%), cardiovascular disease (37,7%), diabetes mellitus (16,39%), and chronic pulmonary disease (16,39%). Table 8. shows comorbidities seen in patients with hypersomnia. The most prevalent comorbidities in patients with hypersomnia in our study group are arterial hypertension (39,6%), cardiovascular disease (37,5%), and chronic kidney disease (14,6%). In our study 59% of patients with sleep disorder reported dyspnea, 78% had pneumonia, 72% were hospitalized, of which 2 patients ended up in Respiratory intensive care and were treated with mechanical ventilation (Table 9.). In the patient group with hypersomnia, 46% of patients reported dyspnea, 64% had pneumonia, 48% were hospitalized of which one patient was hospitalized in Respiratory intensive care, and did not receive treatment with mechanical ventilation.

Table 1. Prevalence of men and women with sleep disorder

			Men	Women	Total	
Sleep disorder	Yes	Number	33	28	61	
		%	19,1%	17,1%	18,1%	X2=0,113
	No	Number	140	136	276	P=0,737
		%	80,9%	82,9%	81,9%	
Total			173	164	337	

Table 2. Prevalence of men and women with hypersomnia

			Men	Women	Total	
Sleepines/hypersomnia	Yes	Number	15	33	48	X2=8,125
		%	8,7%	20,1%	14,2%	P=0,004
	No	Number	158	131	289	
		%	91,3%	79,9%	85,8%	
Total			173	164	337	

Table 3. Association of age, and BMI, with sleep disorder.

	Sleep disorders			
	No	Yes	Z	P
Age	**66 (53-77;18-100)**	**61 (54-70;30-88)**	**2,6**	**0,009**
BMI	**27 (25-30;17-44)**	**29 (26-33;18-43)**	**3,5**	**<0,001**

Quantitative data are shown as median (Q1-Q3;min-max). Comparison is done by Mann-Whitney test.

Table 4. Association of age, and BMI with sleepiness/hypersomnia.

	Sleepiness/hypersomnia			
	No	Yes	Z	P
Age	**66 (55-77;18-100)**	**57 (41-68;18-93)**	**4,3**	**<0,001**
BMI	28 (25-30;17-43)	27 (23-32;17-44)	0,157	0,875

Quantitative data are shown as median (Q1-Q3;min-max). Comparison is done by Mann-Whitney test.

Table 5. Association of pneumonia with sleepiness/hypersomnia

			Pneumonia		Total	
			Yes	No		
Sleepiness/hypersomnia	Yes	Number	31	17	48	
		%	14,4%	13,9%	14,2%	X2=0,000
						P=1,000
	No	Number	184	105	289	
		%	85,6%	86,1%	85,8%	
Total			215	122	337	

Table 6. Association of pneumonia with sleep disorder

			Pneumonia		Total	
			Yes	No		
Sleep disorder	Yes	Number	**48**	**13**	**61**	**X2=6,385**
		%	**22,3%**	**10,7%**	**18,1%**	**P=0,012**
	No	Number	167	109	276	
		%	77,7%	89,3%	81,9%	
Total						

Table 7. Comorbidities seen in patients reporting sleep disorder

Comorbidities (Sleep disorder)	
Arterial hypertension	33/61 (54,09%)
Diabetes mellitus	10/61 (16,39%)
Cardiovascular disease	23/61 (37,7%)
Chronic kidney disease	2/61 (3,27%)
Chronic liver disease	0/61 (0%)
Chronic pulmonary disease	10/61 (16,39%)
Anemia	3/61 (4,91%)
Cancer	5/61 (8,19%)
Imunosupresive disease	4/61 (6,55%)

Table 8. Comorbidities seen in patients reporting hypersomnia

Comorbidities (Sleepines/hypersomnia)	
Arterial hypertension	19/48 39,6%
Diabetes mellitus	6/48 12,5%
Cardiovascular disease	18/48 37,5%
Chronic kidney disease	7/48 14,6%
Chronic liver disease	0/48 0%
Chronic pulmonary disease	4/48 8,3%
Anemia	3/48 6,3%
Cancer	4/48 8,3%
Imunosupresive disease	5/48 10,4%

Table 9. Manifestations of COVID 19 in patients with sleep disorder

Patients with Sleep disorder	
Dispnea	36/61 (59,01%)
Pneumonia	48/61 (78,68%)
Cardiovascular disease (MI, rhythm disorder)	2/61 (3,27%)
Renal insuficiency/dialisis	2/61 (3,27%)
Coagulation disorder (pulmonary embolism)	1/61 (1,6%)
Hospitalised patients	44/61 (72,13%)
Patients in IC	2/61 (3,27%)
Patients on mechanical ventialation	2/61 (3,27%)

Table 10. Manifestations of COVID 19 in patients with hypersomnia

	Patients with Sleepiness/hypersomnia
Dispnea	22/48 (45,8%)
Pneumonia	31/48 (64,6%)
Cardiovascular disease (MI, rhythm disorder)	1/48 (2,1%)
Renal insuficiency/dialisis	1/48 (2,1%)
Coagulation disorder (pulmonary embolism)	1/48 (2,1%)
Hospitalised patients	23/48 (47,9%)
Patients in IC	1/48 (2,1)
Patients on mechanical ventilation	0/48 (0%)

Discussion

During the time of our study most of the papers published were reporting sleep disorders in the general population, and/or health care workers (16,17,18). Lack of studies reporting the prevalence of sleep disorders in COVID 19 positive patients, or discrepancies between different countries urged us in trying to discern the prevalence of sleep disorders in COVID 19 positive patients who came to ED of UH Dubrava looking for medical assistance. Our center being one of the largest regional hospitals dedicated to treating COVID 19 positive patients was an ideal research site for this subject. Not surprisingly sleep disorders being insomnia or hypersomnia were prevalent in little over a third of COVID 19 positive patients in our study (109 of 337, 32,34%). 61 patients (18%) reported sleep disorder/insomnia, 42 (14%) reported hypersomnia during the day/night cycle, while 14 (4,1%) patients reported both insomnia and hypersomnia. Prevalence of sleep disorder/insomnia in our population sample was lower for less than half compared to a meta-analysis done by Deng et al. in which the overall prevalence of sleep disorder is reported to be in 34% of patients (19). Those values varied between different countries with one study in Turkey which reported sleep disorder in 13% of their patients (20). A study done by Liguori et al. reported that sleep disorder was the most reported subjective neurological symptom with the prevalence of 49,51%, while hypersomnia was present in 34/103 (33,01%) of patients (21). When supplementary asking our patients about the nature of their sleep disorder (data not presented) most of them believed that said problem is caused by constant unexplained restlessness, fear of respiratory decline during sleep, and physical discomfort caused by illness with meager amounts of sleep being constantly fragmented by waking. When asked about hypersomnia, patients tried to rationalize it with a feeling of constant tiredness which can be explained by sickness behavior. When comparing our results concerning insomnia in COVID 19 patients to idiopathic insomnia numbers they are somewhat similar with 24% of subjects reporting insomnia in one study (22), 25% in a study done on German citizens (23), 20,3% of Japanese outpatients (24), 17% of a sample of South Korea general population (25), and 11,7% on a sample of Norwegian population (26). Even though prevalence numbers of insomnia in COVID 19 patients in our study were not so different from insomnia prevalence in the general population other characteristics of insomnia in COVID 19 were different, and will be presented as follows.

There was no statistically significant difference in sleep disorder prevalence between men and women in our study ($\chi 2$ = 0,113, p = 0,737) which is following the aforementioned metaanalysis by Deng et al. An interesting observation can be made by this result being that insomnia is usually more prevalent in women while in our study slightly more men reported insomnia compared to women (not statistically significant) (27).

In our study women reported hypersomnia two times more often than men, which is following Liguori et al. study. Several possible explanations for this result come to mind. Perhaps propensity to an increased immune response in acute answer to viral infection attributed to women is an answer, and with it increased fatigue and neurocognitive symptoms of sickness behavior also being more reported by women. (28,29). When comparing between different age groups we found that sleep disorder was more prevalent in middle age patients with COVID 19 compared to patients of older age. According to the epidemiology of insomnia, it is usually more prevalent in older age, but then again insomnia in older age is attributable to inactivity, a decrease of social life, comorbidities, and mental disorders, all of which has transferred to younger age groups with the current pandemic environment. Thus perhaps younger age groups are more sensitive to new-onset insomnia afflicted by COVID 19 (27). Hypersomnia was also more prevalent in patients who fall in the middle age group com-

pared to patients of older age. Another interesting observation can be made with this result being that hypersomnia is usually attributed to sickness behavior, and/or increased depression both of which are more often found in the subject of older age. (30). We found that sleep disorders were more prevalent in patients with higher BMI scores. Even though both analyzed patient groups belonged to the overweight group, a slightly higher BMI score was seen in patients having sleep disorder. Considering how increased weight was a risk factor for a more severe form of COVID 19, it could be a possibility that a trend towards obesity with COVID 19 expects an increased chance of developing a sleep disorder. With hypersomnia, we did not find a significant association with BMI score.

In our study, there was no association between the prevalence of hypersomnia and the prevalence of pneumonia. There was a significant association of sleep disorder with pneumonia. This is in agreement with previous studies which ascertain that when an inflammation passes a certain threshold and becomes more severe same cytokines which facilitate sleep become a source of sleep fragmentation (13). When it comes to comorbidities a slightly higher percentage of them is seen in the group of patients with a sleep disorder, with the chronic pulmonary disease more prevalent in the sleep disorder group, while chronic kidney disease is more prevalent in the hypersomnia group.

Also when it comes to the severity of the COVID 19 clinical picture higher percentage of reported dyspnea and pneumonia is seen in the sleep disorder group compared to the hypersomnia group. A greater percentage of hospitalized patients is seen in a group of patients with sleep disorder compared to a group of patients with hypersomnia. While we examined patients before their hospitalization, a study done by Zhang and colleagues has shown that hospitalized patients with poor sleep tend to have worse clinical prognoses (31).

Conclusion

Among many things COVID 19 certainly affects sleep, and in some ways differently than we were accustomed to. With proposed neuroinvasive properties of SARS CoV - 2, immunological interaction, and psychological effect sleep disorders have shifted from usual older age groups to younger ones. Age, gender, and presence of pneumonia had an effect on the prevalence of insomnia/hypersomnia in our study group.

Limitations of our study were that we did not use sleep related specific questionnaires, our study was a monocentric one, and only those patients which had atleast one neurological symptom were examined. Nevertheless our study shows that sleep disorders in COVID 19 patients are a significant, prevalent symptom of COVID 19 which perhaps has an effect on the outcome of disease.

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