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Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine

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Aims
We performed a prospective cohort study to gain more insight into risk factors for neuropsychiatric effects of mefloquine among tourists travelling to tropical areas.

Methods
We enrolled all patients who consulted the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases Rotterdam for mefloquine prophylaxis during the period between 1 May 1999 and 7 March 2000. Each patient was followed from baseline (prior to starting mefloquine) up to 3 weeks after starting weekly intake of 250 mg mefloquine. We compared the intraindividual change in scores between baseline and follow-up visit on the Dutch shortened Profile of Mood States, and on the Continuous Performance Test (CPT) which measures sustained attention.

Results
The final cohort consisted of 151 subjects with a mean age of 38 years. In this population, a significant impairment of mood state was observed in those with a body mass index (BMI) ≤ 20 kg m^{-2}. Stratification for gender showed that the total mood disturbance in females in the lowest BMI category significantly increased by 8.42 points [95% confidence interval (CI) 3.33, 13.50], whereas BMI did not affect the risk in males. Stratification for history of use of mefloquine showed that the risks were highest in first-time users. Analyses of the CPT showed that reaction time in women with a BMI ≤ 20 kg m^{-2} increased significantly by 22.5 ms (95% CI 7.80, 37.20), whereas reaction time in men showed a slight and nonsignificant decrease.

Conclusion
Risk factors for mefloquine-associated neuropsychiatric adverse events and concentration impairment are female gender, low BMI, and first-time use. The frequency of neuropsychiatric effects is highest in women with a BMI ≤ 20 kg m^{-2}.

Introduction

In many countries, mefloquine is currently the prophylactic drug of choice for travellers staying in areas of high risk of exposure to chloroquine-resistant falciparum malaria [1].

Since 1992, case reports of neuropsychiatric events in the medical literature and widespread media attention have influenced clinical and public opinion concerning the use of antimalarials [2–5]. Risk factors for neuropsychiatric adverse events attributed to mefloquine, however, have not been well characterized. Nevertheless, mefloquine is contraindicated in persons with a history of seizures or a history of psychiatric disease [1]. Moreover, it has been suggested that neuropsychiatric adverse effects by mefloquine are more frequent in women than in men [6–10]. Recently, we performed a study in which we confirmed the relatively high frequency of neuropsychiatric adverse events in women on mefloquine [11]. Because mefloquine has a high apparent volume of distribution, the amount of fat tissue might be associated with neuropsychiatric adverse events. Therefore, we investigated whether body mass index (BMI) can modify the neuropsychiatric effects of mefloquine and whether such an effect is different between males and females.

Methods

We conducted a prospective cohort study in the Travel Clinic of the Havenziekenhuis & Institute for Tropical Diseases Rotterdam, the Netherlands. The study was approved by the local Ethics Committee.

Cohort definition

Our study population consisted of all persons who intended to travel to tropical areas and who consulted the Travel Clinic for required vaccinations and mefloquine prophylaxis during the study period between 1 May 1999 and 7 March 2000. Each person was recruited at the first visit for travel advice during which they were asked for written informed consent. Follow-up ended at a scheduled visit, 2 or 3 weeks after starting chemoprophylaxis but always prior to departure to the tropics. We included in the cohort all subjects who received a prescription for mefloquine (one tablet of 250 mg per week). Persons who had either one or more contraindications for mefloquine (i.e. history of convulsions, psychosis or depression, known allergy or sensitivity to mefloquine, concurrent use of cardiovascular medication) were not included. Subsequently, we excluded subjects who had used mefloquine in the preceding 2 months or subjects who had other risk factors for concentration impairment (e.g. use of opioids, hypnotics or tranquillizers during the 2 weeks prior to testing, use of alcohol 4 h prior to testing). Previous exposure to mefloquine was assessed by questionnaire at baseline. Use of mefloquine during the study period was assessed by means of a diary sheet, on which patients were asked to fill in time of intake during follow-up.

Outcome

Our first outcome measure was the intraindividual change in score of the validated Dutch shortened Profile of Mood States (POMS). The POMS is a validated questionnaire for the measurement of subjective mood. The POMS consists of 32 questions and is designed to measure feelings on five subscales: tension, depression, anger, fatigue, and vigour. The POMS answers are graded on a 5-point scale ranging from 'not at all' (scale 0) to 'extremely' (scale 4) [12]. A composite overall score for total mood disturbance (TMD) was calculated by summing the raw scores across the categories tension, anger, fatigue and depression and subtracting vigour. The calculated total score ranges from −20 to +108, and an increase of the composite score on the POMS reflects an impaired mood state. All subjects were asked to register in a diary all adverse events that were encountered during the first 3 weeks of use of mefloquine.

Our second outcome comprised the intraindividual change in sustained attention [Continuous Performance Test (CPT)] as measured according to the validated Neurobehavioural Evaluation System (NES). The NES is a series of computerized tests designed to provide quantitative neurobehavioural outcomes [13, 14]. A negative value on the CPT indicates that the reaction time increased between the two measurements, whereas a positive difference indicates that the reaction time decreased. For every subject, the reference score was assessed before start of therapy (baseline measurement) and the index score after the third tablet of mefloquine (index measurement).

Covariates

Data on weight, height, demographics, education, travel destination, and chronic comorbidity were gathered at baseline. At the start and the end of follow-up, we collected information on all time-dependent risk factors potentially related to the outcomes on the CPT and POMS. These included use of alcohol, coffee, comedication and illicit drugs.

Analysis

The primary comparison comprised the intraindividual change (delta) in the scores on the POMS, and sustained

attention between baseline measurement and the end of follow-up. The baseline measurement was used as a reference. Univariate analyses regarding the change within subjects were conducted by means of paired sample *t*-tests. Linear regression models were used to study the association between the changes in scores and comorbidity, age and gender. In a second step, we identified by interaction terms whether the intraindividual effects were modified by gender, age, BMI in kg m^{-2}, and previous use of mefloquine. In case of statistically significant interaction, we stratified on this item. In order to study the association between time-dependent covariates such as use of coffee and medication and the change in scores, we used the general linear model for repeated measures. All tests were two-sided with rejection of the null hypothesis at a *P*-value <0.05. As we calculated that the study would require at least 150 participants to be able to demonstrate a statistically significant increase of the outcome total mood disturbance (TMD), the objective was to include at least 200 subjects.

Results

In this cohort, 200 subjects were enrolled, of whom 179 (89.5%) completed follow-up. Reasons for loss to follow-up were: withdrawal of informed consent ($n = 12$), neuropsychiatric adverse effects ($n = 5$), cancelling of the trip ($n = 3$) and moving to another part of the Netherlands ($n = 1$). Of the 21 subjects dropping out, nine (42.9%) were female and 12 (57.1%) were males. Completers were significantly older than dropouts (39 *vs.* 31 years, $P = 0.008$) and had a higher BMI (24.12 *vs.* 21.94, $P = 0.009$). Fifty-eight subjects reported neuropsychiatric adverse events, notably insomnia ($n = 23$), headache ($n = 15$), fatigue ($n = 14$), dizziness ($n = 13$), abnormal dreams/nightmares ($n = 12$), and anxiety/depression/emotional lability ($n = 9$). There were no differences regarding baseline scores on the domains anger, vigour, fatigue and TMD. Depression (0.53 *vs.* 1.57, $P = 0.022$) and tension (1.86 *vs.* 3.19, $P = 0.023$), however, differed significantly between completers and noncompleters. Furthermore, we excluded 28 subjects because they either did not return their diary sheet or had not used three tablets of mefloquine. Hence, the final cohort consisted of 151 subjects, all Caucasians, with a mean age of 38.4 years (SD 12.7 years). General characteristics of the study population are presented in Table 1. Females had a significantly lower BMI than males ($P = 0.009$). Table 2 shows the effect of BMI on the intraindividual change in scores on the POMS. Mod-

Table 1
General characteristics of the study population

	Total ($n = 151$)	Males ($n = 78$)	Females ($n = 73$)
Age in years (range)	38.4 (11–68)	39.9 (11–68)	36.7 (15–59)
BMI (kg m^{-2}) mean (range)*	24.0 (15.8–35.8)	24.7 (15.8–35.8)	23.2 (17.0–31.3)
≤ 20	17 (11.5%)	5 (6.6%)	12 (16.7%)
21–25	78 (52.7%)	39 (51.3%)	39 (54.2%)
> 25	53 (35.8%)	32 (42.1%)	21 (29.2%)
*Higher education**			
Primary/vocational education	14 (9.4%)	10 (13.2%)	4 (5.5%)
Secondary/vocational education	64 (43.0%)	33 (43.4%)	31 (42.4%)
College/university	71 (47.6%)	33 (43.4%)	38 (52.1%)
*Marital status**			
Unmarried	59 (39.9%)	31 (41.3%)	28 (38.3%)
Married/living together	86 (58.4%)	42 (56.0%)	44 (60.3%)
Divorced	3 (2.0%)	2 (2.7%)	1 (1.4%)
Smoking			
Yes	40 (26.5%)	21 (26.9%)	19 (26.0%)
No	111 (73.5%)	57 (73.1%)	54 (74.0%)
*Medical complaints**			
Yes	13 (8.7%)	5 (6.4%)	8 (11.1%)
No	137 (91.3%)	73 (93.6%)	64 (88.9%)

**Numbers do not add up to total since some subjects did not answer all questions. Body mass index (BMI) in females significantly lower than in males (P = 0.009).*

Table 2
Association between body mass index (BMI) and Profile of Mood States (POMS) stratified for gender

	Total population Mean difference (95% CI)*	Males Mean difference (95% CI)*	Females Mean difference (95% CI)*
Tension			
BMI ≤20	–0.35 (–1.57, 0.87)	0.20 (–2.02, 2.42)	–0.58 (–2.24, 1.07)
21–25	0.38 (–0.30, 1.10)	–0.26 (–1.08, 0.57)	1.03 (–0.06, 2.11)
>25	–0.17 (–0.95, 0.61)	0.31 (–0.76, 1.39)	–0.90 (–2.00, 0.20)
Depression			
BMI ≤20	0.29 (–0.40, 0.99)	–	0.42 (–0.61, 1.45)
21–25	0.58 (–0.16, 1.31)	0.05 (–0.34, 0.44)	1.10 (–0.33, 2.53)
>25	0.04 (–0.34, 0.42)	0.22 (–0.24, 0.67)	–0.24 (–0.94, 0.47)
Anger			
BMI ≤20	1.59 (–0.59, 3.76)	0.20 (–0.36, 0.76)	2.17 (–0.99, 5.32)
21–25	–0.47 (–1.60, 0.65)	–1.38 (–2.82, 0.05)	0.44 (–1.30, 2.17)
>25	0.23 (–0.40, 0.85)	0.16 (–0.72, 1.03)	0.33 (–0.60, 1.27)
Fatigue			
BMI ≤20	**2.53 (0.60, 4.46)**	0.00 (–1.52, 0.52)	**3.58 (1.5, 6.12)**
21–25	**1.08 (0.15, 2.01)**	0.56 (–0.48, 1.62)	**1.59 (0.02, 3.16)**
>25	–0.09 (–0.80, 0.99)	0.75 (–0.49, 1.99)	–0.90 (–2.14, 0.33)
Vigour			
BMI ≤20	**–2.06 (–3.44, –0.68)**	–0.20 (–1.82, 1.42)	**–2.83 (–4.59, –1.08)**
21–25	–0.14 (–1.05, 0.77)	0.03 (–1.39, 1.34)	–0.26 (–1.52, 1.01)
>25	1.04 (–0.08, 2.15)	0.78 (–0.39, 1.95)	1.43 (–0.89, 3.74)
Total mood disturbance			
BMI ≤20	**6.12 (2.17, 10.07)**	0.60 (–2.39, 3.59)	**8.42 (3.33, 13.50)**
21–25	1.71 (–1.33, 4.74)	–1.00 (–3.73, 1.73)	4.41 (–1.03, 9.85)
>25	–0.85 (–3.25, 1.55)	0.66 (–2.54, 3.85)	–3.14 (–6.85, 0.56)

**Mean difference in score (index measurement – baseline measurement) with significant changes given in bold.*

ification of the effect of mefloquine by BMI was observed only among women. Women in the lowest BMI category decreased in vigour, and the TMD increased significantly by 8.42 [95% confidence interval (CI) 3.33, 13.50] points. In males no association was observed between the intraindividual change in TMD and BMI. Other risk factors that may affect mood such as age and smoking were not associated with the change in TMD or the change in any of the domains.

Table 3 shows the effect modification by a history of use of mefloquine on the change in mood due to mefloquine by BMI. No changes in mood were observed in subjects who had used mefloquine more than 2 months preceding current use. In first-time users, however, a significant increase in the domain fatigue, the TMD, and a decrease in the domain vigour were observed, but only among women. These effects were most pronounced in the lowest BMI tertile, a little smaller in the mid tertile, and not present among females in the highest BMI tertile. The TMD also showed a significant increase of 9.09 points (95% CI 3.70, 14.49) in first-time female users with a BMI ≤20 kg m^{-2}. In comparison with individuals with a BMI >25 kg m^{-2}, individuals with a BMI ≤20 kg m^{-2} had a 3.1 times higher (95% CI 1.1, 8.5) risk of neuropsychiatric adverse events.

There was no significant change in reaction time during the study period, nor was there a significant difference in this regard between males and females. There was, however, a significant increase in CPT in women with a low BMI of 22.5 ms (95% CI 7.8, 37.20), but precision was low (Table 4).

Discussion

In this study, two important effect modifiers for neuropsychiatric adverse events and concentration impairment were identified. Apart from gender, the main effect modifier for neuropsychiatric adverse events as well as concentration impairment was BMI. Subjects with a BMI ≤20 kg m^{-2} experienced significant impairment of mood state and a significant increase in reaction time, and

Table 3
Association between previous use of mefloquine, body mass index (BMI) and Profile of Mood States (POMS)*

	Total population		Males		Females	
	With previous use	Without previous use	With previous use	Without previous use	With previous use	Without previous use
Tension						
BMI ≤20	0.33 (–7.26, 7.92)	–0.50 (–1.84, 0.84)	2.00 (–10.71, 14.71)	–	–	–0.36 (–2.12, 1.40)
21–25	0.19 (–0.84, 1.21)	0.52 (–0.42, 1.46)	–0.71 (–2.31, 0.88)	0.00 (–1.02, 1.02)	0.89 (–0.50, 2.27)	1.14 (–0.59, 2.88)
>25	0.36 (–1.21, 1.94)	–0.55 (–1.33, 0.23)	0.27 (–2.03, 2.56)	0.35 (–0.40, 1.10)	0.57 (–1.27, 2.41)	**–1.64 (–2.99, –0.29)**
Depression						
BMI ≤20	–0.33 (–1.77, 1.10)	0.43 (–0.41, 1.27)	–	–	–	0.55 (–0.55, 1.64)
21–25	0.16 (–0.42, 0.74)	0.87 (–0.32, 2.06)	0.07 (–0.35, 0.49)	0.04 (–0.55, 0.63)	0.22 (–0.81, 1.25)	1.86 (–0.72, 4.43)
>25	–0.27 (–0.96, 0.41)	0.26 (–0.20, 0.71)	0.13 (–0.37, 0.64)	0.29 (–0.49, 1.08)	–1.14 (–3.24, 0.95)	0.21 (–0.25, 0.68)
Anger						
BMI ≤20	0.67 (–2.20, 3.54)	1.79 (–0.89, 4.47)	–	0.33 (–1.10, 1.77)	–	2.18 (–1.32, 5.68)
21–25	–1.78 (–3.74, 0.18)	0.43 (–0.89, 1.76)	–2.86 (–5.89, 0.17)	–0.56 (–2.11, 0.99)	–0.94 (–3.71, 1.82)	1.62 (–0.66, 3.90)
>25	0.00 (–1.09, 1.09)	0.39 (–0.40, 1.17)	–0.33 (–1.88, 1.21)	0.59 (–0.46, 1.63)	0.71 (–0.67, 2.10)	0.14 (–1.19, 1.48)
Fatigue						
BMI ≤20	1.00 (–1.48, 3.48)	**2.86 (0.51, 5.29)**	1.00 (–11.71, 13.71)	–0.67 (–2.10, 0.77)	–	**3.82 (1.07, 6.57)**
21–25	0.90 (–0.43, 2.24)	1.20 (–0.12, 2.52)	0.07 (–1.80, 1.95)	0.84 (–0.51, 2.19)	1.56 (–0.42, 3.53)	1.62 (–0.93, 4.17)
>25	0.64 (–0.99, 3.69)	–0.29 (–1.36, 0.78)	0.93 (–1.11, 2.98)	0.59 (–1.11, 2.28)	0.00 (–3.50, 3.50)	**–1.36 (–2.53, –0.19)**
Vigour						
BMI ≤20	–0.67 (–4.46, 3.13)	**–2.36 (–3.98, –0.73)**	0.00 (–12.71, 12.71)	–0.33 (–4.13, 3.46)	–	**–2.91 (–4.84, –0.97)**
21–25	0.59 (–0.74, 1.92)	–0.65 (–1.90, 0.60)	0.36 (–1.35, 2.06)	–0.24 (–2.23, 1.75)	0.78 (–1.33, 2.89)	–1.14 (–2.71, 0.42)
>25	1.86 (–0.04, 3.69)	0.45 (–0.99, 1.90)	1.60 (–0.39, 3.59)	0.06 (–1.39, 1.51)	2.43 (–2.49, 7.35)	0.93 (–2.01, 3.87)
Total mood disturbance						
BMI ≤20	2.33 (–1.46, 6.13)	**6.93 (2.16, 11.70)**	3.00 (–9.71, 15.71)	–1.00 (–3.48, 1.48)	–	**9.09 (3.70, 14.49)**
21–25	–1.13 (–5.55, 3.30)	3.67 (–0.49, 7.83)	–3.79 (–9.51, 1.94)	0.56 (–2.41, 3.53)	0.94 (–5.90, 7.79)	7.38 (–1.17, 15.94)
>25	–1.14 (– 5.54, 3.26)	–0.65 (– 3.55, 2.26)	–0.60 (– 6.49, 5.29)	1.76 (–1.90, 5.43)	–2.29 (–10.66, 5.93)	–3.57 (–8.23, 1.08)

**Mean difference in score (index measurement – baseline measurement) with significant changes given in bold.*

Table 4
Mean difference in continuous performance (CPT) in ms after three tablets of mefloquine*

	Total (n = 149) Mean difference (95% CI)	Males (n = 76) Mean difference (95% CI)	Females (n = 73) Mean difference (95% CI)
CPT total	–0.40 (–4.48, 3.69)	–2.53 (–8.17, 3.11)	1.82 (–74.19, 7.84)
BMI ≤20	15.00 (–0.04, 30.04)	–3.00 (–49.11, 43.11)	**22.50 (7.80, 37.20)**
21–25	–1.81 (–7.25, 3.63)	–1.26 (–8.57, 6.06)	–2.36 (–10.75, 6.03)
>25	–4.75 (–11.48, 1.99)	–6.23 (–15.60, 3.14)	–2.62 (–12.91, 7.67)

**Statistically significant changes are given in bold.*

these effects were further modified by gender. The largest effects were observed in females with a low BMI who were first-time users of mefloquine.

Mefloquine is distributed extensively over tissues and the apparent volume of distribution ranges from 13 to 40 l kg^{-1} with a mean of 20 l kg^{-1}. It is highly protein bound (98%) and may accumulate in erythrocytes (Product information Lariam®, Roche, the Netherlands), and is predominantly excreted in the bile and faeces. Considerable pharmacokinetic differences are reported between persons of different ethnic backgrounds regarding both systemic clearance and apparent volume of distribution [15]. For example, higher serum levels of mefloquine in Asians have been explained to be secondary to a relatively lower body fat content or differences in the enterohepatic circulation of mefloquine [16]. However, we could not investigate the effect of ethnicity since our population was entirely Caucasian. Our data suggest that adverse events occur only in subjects with a low BMI. This may be explained by a lower volume of distribution and consequently by potentially higher plasma levels of mefloquine. However, we observed a significant interaction between gender and BMI, as low BMI was a risk factor only in females. This suggests that gender-related differences in pharmacokinetics may also play a role. Although reduction of the dose of mefloquine in women with a BMI ≤20 kg m^{-2} might diminish the occurrence of these effects, the effectiveness of chemoprophylaxis at lower doses might be less. Future studies should provide data on the relationship between dose reduction, serum levels of mefloquine, effectiveness and the occurrence of adverse events.

Before drawing conclusions from the results of our study we should emphasize some potential limitations. The study population comprised persons who intended to visit tropical areas, and were advised to use mefloquine for prophylaxis of malaria. The follow-up measurements were conducted after intake of the third tablet of mefloquine prior to departure. Mefloquine is the only prophylactic drug which has a run-in period. Although a run-in period of 3 weeks allowed us to study the adverse events during the period that the subjects were still in the Netherlands, we could not use an external comparison group. Furthermore, depletion of susceptibles (the so-called 'healthy user effect') might have influenced the overall results of our study as many users are regular visitors to tropical areas. Therefore, we stratified for history of use of mefloquine which showed that the impairment of neuropsychological tests occurred in first-time users of mefloquine, especially in those in the lowest BMI tertile. Studies that do not take into account prior use of mefloquine may therefore underestimate the effect of mefloquine on the neuropsychiatric tests and reaction time. In our study, we focused on neuropsychiatric tests as a primary outcome. These tests have been validated and are a sensitive measure of mood changes. Earlier, we demonstrated that individuals on mefloquine with neuropsychiatric adverse events showed a significant increase in the domains depression, fatigue and TMD, whereas in individuals without adverse events no changes occurred [11]. Hence, any misclassification of outcome is probably modest. Moreover, self-reported neuropsychiatric adverse events also occurred significantly more often in individuals with a low BMI, which is in line with the changes in the neuropsychiatric tests.

In conclusion, we found that mefloquine-associated neuropsychiatric adverse events and concentration impairment were modified by gender and BMI. Females encountered more adverse events than males and these effects were most pronounced in women with a BMI ≤20 kg m^{-2}. Since this might be compatible with a relatively low volume of distribution and relatively high plasma levels, more studies should focus on the relationship between the serum concentration of mefloquine and

its carboxylic acid metabolite and the occurrences of neuropsychiatric adverse events.

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