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ORIGINAL ARTICLE

Identification of factors associated with minimal erythema dose variations in a large-scale population study of 22 146 subjects

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Abstract

Background Minimal erythema dose (MED) has substantial inter- and intraindividual variations, reflecting the influence of very diverse factors. However, related studies showed little consistency probably because of their limited sample size.

Objective To identify the factors associated with MED variations in a large-scale population study.

Methods The MED test was performed by following the international standard procedure on 22 146 subjects. The results were analysed in adjusted multivariable linear and logistic regression models.

Results This large-scale study revealed that lower MED was consistently associated with lighter skin [β-coefficient = −0.33, 95% confidence interval (CI) −0.36 to 0.30, $P = 6.41 \times 10^{-84}$]. Females had significantly higher MED than male (β = 0.91, 0.32–1.50, $P = 2.93 \times 10^{-3}$). Stratified analyses showed that MED was not associated with age [female: odds ratio (OR) = 0.99, 0.98–1.01; male: OR = 0.99, 0.97–1.00]. MED was lower in summer than in other seasons (spring: OR = 1.08, 1.06–1.11; autumn: OR = 1.11, 1.08–1.13; winter: OR = 1.20, 1.18–1.22). Furthermore, MED was associated with air temperature (β = −0.36, −0.49 to 0.23, $P = 4.81 \times 10^{-8}$) and air pressure (β = −0.64, −0.82 to 0.46, $P = 8.01 \times 10^{-12}$) in summer only while not in other seasons.

Conclusions This study provides unprecedented evidence that MED is associated with skin colour, sex, season and meteorological factors, but not with age.

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Conflicts of interest

None declared.

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Introduction

Minimal erythema dose (MED) is defined as the dose of UVB irradiation after which a minimally perceptible skin erythema can be detected.[1] Determination of MED is a *conditio sine qua non* for UVB phototherapy of skin diseases,[2,3] for the diagnosis of photodermatosis,[4,5] and for the determination of the Sun Protection Factor or, in other words, the efficacy testing of commercial sunscreen products.[6] Given that worldwide $7.1 billions of sunscreens were sold in 2017,[7] it is evident that standardization of MED testing is of utmost importance.

In this regard, it has to be noted that MED has substantial inter- and intraindividual differences. At least for the interindividual differences, a significant part of the variation in Caucasians can be attributed to differences in Fitzpatrick skin types (i.e. the higher the skin type, the higher the MED[8,9]), but other influencing factors are likely to contribute as well. According to the published literature, these might potentially include sex, age, skin colour, season during which the testing was performed, and meteorological factors. However, past studies actually lacked consistency as results had not been reproduced between studies or even opposite results had been reported. For example, a number of studies found higher MED in individuals with darker skin,[10,11] but others reported no correlation between MED and skin colour.[8,12] While it was generally believed that there were no sex differences in MED,[8] there were mixed reports on the effects of age on MED.[13,14] The effects of seasonal factors were also unclear from previous studies.[15–17] Notably, all of the aforementioned studies on MED were based on relatively small sample sizes, ranging from 8 to 355 test subjects. In the present study, we therefore readdressed this important topic by capitalizing on MED data from an unprecedented large sample size of 22 146 Han Chinese individuals.

Materials and methods

Study sample

From April 2012 to December 2017, 22 146 healthy Han Chinese from Shanghai, which were 18–60 years old, were enrolled for MED testing at the Shanghai Skin Disease Hospital. Exclusion criteria were a history of abnormal reactions to sunlight, abnormal skin at the test sites, a history of skin cancer, chronic skin diseases and drug hypersensitivity. The subjects were told not to use drugs for 4 weeks and to avoid sun exposure on their back for 2 months before the study. All subjects provided written informed consent and understood that they could withdraw from the study at any time (Fig. S1, Supporting Information). This study was approved by the institutional ethics committee of the Shanghai Skin Disease Hospital (Approval ID: 2009-01).

MED testing

The MED testing was performed by following the international standard procedure described in ISO 24444:2010.[18] Briefly, each subject received a total of 6 irradiations, which geometrically incremented by a factor of 1.41, on unexposed areas of the lower back from a solar simulator (GS-2004; Aohua Co., Beijing, China), equipped with a 450W xenon lamp and a dichroic mirror. The results were assessed 20 h ± 4 h after exposure, and MED was defined as the lowest irradiation dose, at which skin erythema with clear borders was visible.[18] Visual assessment was performed in sufficient and uniform illumination by two trained observers. There was no significant difference in the readings between the two observers ($P = 0.81$, one-way ANOVA).

Skin colour testing

Skin colour of all subjects was measured by individual topology angle (ITA°) on unexposed area of the lower back using Chromameter CR-400. The ITA° of each subject was calculated based on the measured L^* and b^* values according to the formula: $ITA^\circ = [\arctan \frac{L^*-50}{b*}] \times \frac{180}{\pi}$.

Meteorological data

Meteorological data were obtained from the meteorological station of Baoshan District in Shanghai, China. The data included daily temperature, relative humidity and atmospheric pressure in Shanghai from January 2012 to December 2017.

Statistical analysis

Baseline characteristics were presented as means (standard deviation [SD]) for quantitative traits and as numbers (percentages) for categorical variables. Subjects were divided into two groups (i.e. the lower MED group and the higher MED group) according to median MED. Characteristics were compared between the lower MED group and the higher MED group using *t*-tests for continuous variables and chi-squared tests for categorical variables. Multivariable regression models were used to estimate coefficients, odds ratios (ORs) and their 95% confidence intervals (CIs) for skin colour, sex, age, season and meteorological factors. OR was used to confirm the results of linear regression models as MED did not conform to a normal distribution (Anderson–Darling test, $P < 0.05$).

Covariate adjustment included season and meteorological factors in model 1, and further included skin colour, sex and age in model 2. The resulting β-coefficients of regression models represented the unit change in MED (β-unit increase in MED per one-unit increase in related factors); ORs were presented as percentage change of MED from the lower group to the higher group, calculated by the formula: $(OR - 1) \times 100\%$. Significance levels were adjusted with Bonferroni correction for the multiple comparisons. All analyses were performed using software package R (http://www.R-project.org).

Power analysis

The Quanto software (version 1.2.4, http://biostats.usc.edu/Quanto.html) was utilized to estimate the statistical power to detect the associations.[19] Independent variables (i.e. skin colour, age and sex) and meteorological data in Shanghai (i.e. air temperature and air pressure) were used in power analysis. The mean value and SD of MED, sex ratio, the regression coefficient and the SD of each variable were used to calculate the power for the association analysis.

Results

Characteristics of the study population

A total of 22 146 healthy Chinese subjects, including 12 211 males and 9935 females, completed the MED testing between April 2012 and December 2017. Subjects in the higher MED group were more likely to be younger than those in the lower MED group, with a mean age of 38.24 compared to 39.89 years ($P = 2.33 \times 10^{-22}$). In the lower MED group, 47.89% were females compared with 41.84% in the higher MED group ($P = 1.66 \times 10^{-19}$). Subjects in the higher MED group were also likely to have darker skin colour than those in the lower MED group, with the ITA° value of 38.76 compared to 41.26 ($P = 8.41 \times 10^{-74}$). There was no difference in relative humidity of test dates between two groups ($P = 0.07$). On average, air temperature of the test day for the lower MED group was likely to be higher than that for the higher MED group, with a mean value of 19.19 compared to 16.32 degree centigrade ($P = 1.27 \times 10^{-12}$); air pressure of the test day for the lower MED group was likely to be lower than that for the higher MED group, with the mean value of 760.71 vs. 762.71 hPa ($P = 3.59 \times 10^{-11}$; Table 1).

Association between MED and skin colour

In the multivariable regression model adjusting for air temperature, air pressure and season (Table 2, model 1), lower MED was significantly associated with lighter skin colour ($\beta = -0.35$, 95% CI: -0.38 to -0.32, $P = 9.02 \times 10^{-105}$). In the fully adjusted model additionally controlling for individual factors (Table 2, model 2), skin colour was also negatively related to MED with a β of -0.33 (95% CI: -0.36 to -0.30, $P = 6.41 \times 10^{-84}$).

Furthermore, stratified analyses showed that lower MED was significantly associated with lighter skin colour (higher ITA° value) in both males ($\beta = -0.24$, -0.28 to -0.20, $P = 2.59 \times 10^{-30}$) and females ($\beta = -0.33$, -0.39 to -0.28, $P = 4.31 \times 10^{-38}$). We then tested whether the association between MED and skin colour would remain in different skin colour groups. To this end, we defined lighter skin to be equivalent to an ITA° value higher than 41 and darker skin as 41 or lower. Stratified analyses showed that MED was related to skin colour in both darker skin group (male: $\beta = -0.18$, -0.26 to -0.10, $P = 1.02 \times 10^{-5}$; female: $\beta = -0.30$, -0.46 to -0.15, $P = 1.37 \times 10^{-4}$) and lighter skin group (male: $\beta = -0.20$, -0.31 to -0.09, $P = 3.73 \times 10^{-4}$; female: $\beta = -0.35$, -0.45 to -0.26, $P = 7.08 \times 10^{-13}$; Table S1, Supporting Information).

Association between MED and sex

In model 1, MED was lower in females than in males (OR = 0.95, 95% CI: 0.94–0.96). However, compared with females, males had significantly darker skin (-0.44, $P = 2.72 \times 10^{-47}$), and skin colour might thus cover up potential effects of sex on MED. Accordingly, in model 2, which controlled skin colour, females had a significantly higher MED than males (OR = 1.03, 1.01–1.05; Table 2). Moreover, stratified analyses showed that such difference held true for both darker skin group (OR = 1.04, 1.02–1.06) and lighter skin group (OR = 1.04, 1.02–1.07; Table S2, Supporting Information).

Association between MED and age

In model 1, younger subjects were more likely to have higher MED values ($\beta = -1.07$, -1.22 to 0.92, $P = 3.42 \times 10^{-44}$).

Table 1 Baseline characteristics of the study population

Characteristics	All subjects (*n* = 22 146)	Low MED group (*n* = 10 994)	High MED group (*n* = 11 152)	*P*†
MED, mean (SD), mJ/cm^2	27.35 (16.96)	15.36 (3.75)	39.30 (16.56)	–
Age, mean (SD), years	39.07 (12.63)	39.89 (12.56)	38.24 (12.64)	2.33×10^{-22}
Female sex, *n* (%)	9935 (44.86)	529 (47.89)	4643 (41.84)	1.66×10^{-19}
Skin colour, mean (SD), ITA°	39.76 (8.30)	41.26 (8.42)	38.76 (8.06)	8.41×10^{-74}
Relative humidity, mean (SD), %	70.83 (12.73)	70.67 (12.58)	70.98 (12.87)	0.07
Air temperature, mean (SD), °C	17.75 (8.92)	19.19 (8.89)	16.32 (8.71)	1.27×10^{-12}
Air pressure, mean (SD), hPa	761.71 (6.77)	760.71 (6.63)	762.71 (6.75)	3.59×10^{-11}
Season				
Spring, *n* (%)	5832 (26.33)	2669 (24.15)	2694 (24.28)	1.07×10^{-30}
Summer, *n* (%)	6046 (27.30)	2837 (25.67)	2995 (26.99)	
Autumn, *n* (%)	5365 (24.23)	3630 (32.85)	2416 (21.77)	
Winter, *n* (%)	4905 (22.15)	1914 (17.32)	2991 (26.96)	

†Baseline characteristics were compared between the low MED group and the high MED group using *t*-tests for continuous variables and chi-squared tests for categorical variables.
ITA°, individual topology angle; MED, minimal erythema dose.

Table 2 Multivariable regression models for the association between minimal erythema dose (MED) and factors of interest

	β (95% CI)§	*P*-value for β	OR (95% CI)¶	*P*-value for OR
Model 1†				
Skin colour, ITA°	−0.35 (−0.38, −0.32)	9.02×10^{-105}	0.99 (0.99, 0.99)	1.51×10^{-67}
Sex, male vs. female	−2.28 (−2.66, −1.90)	2.91×10^{-31}	0.95 (0.94, 0.96)	2.49×10^{-18}
Age, per 10 years	−1.07 (−1.22, −0.92)	3.42×10^{-44}	0.97 (0.97, 0.98)	3.27×10^{-29}
Model 2‡				
Skin colour, ITA°	−0.33 (−0.36, −0.30)	6.41×10^{-84}	0.99 (0.99, 0.99)	1.23×10^{-57}
Sex, male vs. female	0.91 (0.32, 1.50)	2.93×10^{-3}	1.03 (1.01, 1.05)	3.26×10^{-4}
Age, per 10 years	−0.75 (−0.97, −0.53)	4.11×10^{-11}	0.98 (0.98, 0.99)	3.05×10^{-7}

†Model 1 was adjusted for air temperature, air pressure and season. ‡Model 2 was adjusted for model 1 and for other individual factors (i.e. sex, age, skin colour). §The linear regression β-coefficients were presented as unit change in MED (β-unit increase in MED is associated with per-unit increase in individual factors). ¶The odd ratios of logistic regression were presented as percentage change of MED from the lower group to the higher group, calculated by the formula: (OR − 1) × 100%.
ITA°, individual topology angle.

Table 3 Seasonal difference of minimal erythema dose

Season†	β-value (95% CI)‡	*P*-value for β	OR (95% CI)‡	*P*-value for OR
All subjects				
Spring	0.75 (0.08, 1.43)	0.03	1.08 (1.06, 1.11)	3.19×10^{-16}
Autumn	2.89 (2.22, 3.57)	5.12×10^{-17}	1.11 (1.08, 1.13)	1.40×10^{-24}
Winter	7.31 (6.61, 8.02)	8.05×10^{-92}	1.20 (1.18, 1.22)	1.66×10^{-70}
Seasonal difference in males				
Spring	0.50 (0.35, 1.36)	0.02	1.08 (1.05, 1.10)	1.10×10^{-9}
Autumn	3.36 (2.50, 4.22)	2.06×10^{-14}	1.12 (1.10, 1.15)	3.34×10^{-20}
Winter	7.06 (6.17, 7.94)	3.11×10^{-54}	1.19 (1.16, 1.22)	2.14×10^{-40}
Seasonal difference in females				
Spring	1.12 (0.02, 2.24)	0.01	1.09 (1.06, 1.13)	7.37×10^{-8}
Autumn	2.18 (1.08, 3.28)	1.02×10^{-4}	1.08 (1.05, 1.12)	9.14×10^{-7}
Winter	7.78 (6.64, 8.93)	6.93×10^{-40}	1.22 (1.18, 1.26)	1.47×10^{-31}

†Summer was used as reference in regression models. ‡Models were adjusted for age, sex and skin colour. Threshold of *P*-value in stratified analysis was adjusted by applying a Bonferroni correction ($P = 0.05/2$).

Although age was still negatively related to MED in model 2, β changed to −0.75 (95% CI: −0.97 to 0.53, $P = 4.11 \times 10^{-11}$; Table 2).

Stratified analyses showed that age was not associated with MED in both females (OR = 0.99, 0.98–1.01) and males (OR = 0.99, 0.97–1.00). Within males, stratified analyses by age revealed that MED was associated with age only in age group of 18–30 years (β = −2.50, −3.93 to 1.06, $P = 6.74 \times 10^{-4}$), but the result of OR was inconsistent (OR = 0.96, 0.92–1.01; Table S3, Supporting Information).

Season and meteorological factors

We next analysed seasonal differences by controlling for skin colour, sex and age in a multivariable regression model. MED in summer was significantly lower than in any other seasons (spring: OR = 1.08, 1.06–1.11; autumn: OR = 1.11, 1.08–1.13; winter: OR = 1.20, 1.18–1.22). Moreover, stratified analyses showed that this association was significant in both males (spring: OR = 1.08, 1.05–1.10; autumn: OR = 1.12, 1.10–1.15; winter: OR = 1.19, 1.16–1.22) and females (spring: OR = 1.09, 1.06–1.13; autumn: OR = 1.08, 1.05–1.12; winter: OR = 1.22, 1.18–1.26; Table 3). We also asked if meteorological factors might affect MED. We found that MED was significantly associated with air temperature (β = −0.36, −0.49 to 0.23, $P = 4.81 \times 10^{-8}$) and air pressure (β = −0.64, −0.82 to 0.46, $P = 8.01 \times 10^{-12}$; Table 4) only in summer.

Discussion

We here report results from an unprecedentedly large-scale study of MED determinations in 22 146 healthy Han Chinese subjects. This is the first study with sufficient statistic power to provide resounding evidence for factors associated (or not associated) with MED. For example, with a sample size of 300, which is the largest in previous studies, the statistical power is only

Table 4 Effects of meteorological factors on seasonal difference of minimal erythema dose

Season	β (95% CI)†	*P*-value for β‡	OR (95% CI)†	*P*-value for OR‡
Spring (*n* = 5832)				
Air temperature	−0.14 (−0.27, 0.001)	0.05	0.99 (0.98, 0.99)	0.08
Air pressure	−0.21 (−0.36, −0.06)	0.07	0.99 (0.99, 1.00)	0.01
Summer (*n* = 6046)				
Air temperature	−0.36 (−0.49, −0.23)	4.81×10^{-8}	0.99 (0.98, 0.99)	1.74×10^{-13}
Air pressure	−0.64 (−0.82, −0.46)	8.01×10^{-12}	0.99 (0.98, 0.99)	3.86×10^{-7}
Autumn (*n* = 5363)				
Air temperature	−0.08 (−0.25, 0.09)	0.37	1.00 (0.99, 1.00)	0.81
Air pressure	0.31 (0.11, 0.52)	0.03	1.01 (1.00, 1.01)	0.02
Winter (*n* = 4905)				
Air temperature	−0.06 (−0.31, 0.19)	0.65	1.00 (0.99, 1.01)	0.42
Air pressure	−0.08 (−0.30, 0.14)	0.47	1.00 (1.00, 1.01)	0.90

†Each model was adjusted for age, sex, skin colour and season. ‡Threshold of *P*-values was adjusted by applying a Bonferroni correction (*P* = 0.05/4).

sufficient to detect the association of MED with skin colour, air temperature and air pressure. However, for all the other factors of interest (i.e. sex and age), the statistical power is insufficient, ranging from 7.49% to 16.22% (Fig. S2, Supporting Information). In the present study, with a much larger sample size of 22 146, the statistical power of each association is higher than 99.89%.

Our stratified analyses showed that lower MED was consistently associated with lighter skin in both sexes and in both darker and lighter skin groups. We further found that males had lower MED than females after controlling for skin colour. This is in line with a previous report concluding that males were immunosuppressed by ssUV doses three times lower than those required to immunosuppress females.[20] Both MED and immunosuppression are – at least to a substantial part – mediated via UV radiation-induced nuclear DNA damage,[21,22] which might represent a common denominator, indicating that the MED sex differences found in our and other studies might be due to differences in DNA damage responses between male and female subjects.

Minimal erythema dose was not related to age in both females and males, but marginally associated with age in males in age group of 18–30 years, although no association was found in each of the other age groups. We found that MED in males in age group of 18–30 years was significantly higher than in the other groups (Table S4, Supporting Information). Young males are usually the group with most outdoor activity, and as a consequence, their UV exposure is likely to be the highest, which might decrease their sensitivity to UV irradiation.[17,23]

We also found that MED was significantly lower in summer than in the other seasons. This difference was not due to confounders, such as age, sex and skin colour. One possible explanation might be that sweating, by influencing the hydration of the horny layer of the skin, could decrease the reflection and dispersion of UV radiation and therefore reduce MED.[24] Apparently, people sweat the most in summer, and sweating is affected by both air temperature and air pressure.[25]

In this study, we focused on the influencing factors of our most interest, including skin colour, sex, age, season and meteorological factors. In addition to these factors, several studies reported an association between MED and Fitzpatrick skin types.[8,26] Here, we did not consider Fitzpatrick skin types because in contrast to the other influencing factors, they cannot be objectively determined, and correlations between Fitzpatrick skin types and MED have mainly been shown in Caucasians, whereas our study exclusively involved Han Chinese. Besides, this study is based on Han Chinese subjects. Whether the results are completely reproducible in Caucasian subjects should ideally be explored in large-scale studies in Caucasians in the future.

In conclusion, this study provides unprecedented evidence, based on a large-scale population study of 22 146 subjects, that MED is associated with skin colour, sex, season and meteorological factors, but not with age. These findings should be considered in the study design and interpretation of MED tests.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Flow diagram illustrating the minimal erythema dose testing procedure.

Fig. S2. Power analysis of the associations between MED and factors of interest.

Table S1. Association between MED and skin color in stratified analyses.

Table S2. Sex difference of MED in stratified analysis.

Table S3. Association between MED and age in stratified analyses.

Table S4. MED of each age group in males and females.