Effects of Ethnicity and Gender on Motion Sickness Susceptibility

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Introduction: Susceptibility to motion sickness (MS) is known to be affected by gender and ethnic origin, but whether gender and ethnicity are interacting is unknown. ***Methods:*** We investigated MS development in healthy Caucasian subjects (n = 227), and in subjects of Chinese origin (n = 82). All subjects were exposed to nausea-inducing body rotations in a rotation chair, and rotated around the yaw axis for 5 × 1 min, while they were instructed to move their heads. Prior to rotation, subjects had to fill out a motion-sickness susceptibility questionnaire (MSSQ). Total rotation tolerance time (RT) was noted. Symptom ratings (SR) were performed at the beginning, and immediately after the end of each rotation, and 15 and 30 min later. ***Results:*** The average RT was significantly higher in Caucasian (163 ± 6 s) than in Chinese subjects (111 ± 7 s) ($F = 24.84$, $p < 0.0001$). The adult MSSQ score was significantly lower in Caucasians (17.8 ± 1.1) than in Chinese volunteers (24.2 ± 2.1) ($F = 6.05$, $p = 0.014$). Maximal SR post rotation was similar in Chinese and Caucasian subjects. RT was highly predictable from the MSSQ scores, but separate for both genders. ***Conclusion:*** Susceptibility to MS is affected by both ethnic origin and by gender in a rather complex fashion. The most reliable prediction of RT can be based on the individual's history as assessed by the MSSQ.

Keywords: nausea, vomiting, rotation chair, screening, ethnicity, gender.

FOR MOST CLINICAL conditions and procedures that entail a risk of developing nausea and vomiting (N&V), e.g., post-operative (23), chemotherapy (5), under opioids (3), during angiography (17), and in functional bowel disorder (14), N&V is reported to be higher in women than in men. Even under natural conditions, e.g., during sea travel (13) or during turbulence in aircrafts (28), women report more N&V than men. However, when susceptibility to developing N&V was tested between the genders during experiments involving nauseogenic body rotation or pseudo-rotation (vection), gender effects could not be confirmed (4,20). Instead, it was found that although women might report more subjective symptoms of N&V as recorded on symptom ratings (SR) scales (e.g., 8), the biological markers of N&V or tolerance to rotation (RT) were not altered.

Gender differences have occasionally been attributed to differences in symptom awareness and the willingness to acknowledge such symptoms in socially controlled situations (12). In one experiment, however, the gender of the experimenter did not influence the SR of the volunteers (8), leaving the question open as to whether any gender difference reflects a response bias or is due to biological differences in susceptibility to motion.

Gender influences not only the occurrence of symptoms of N&V but also the effectiveness of treatment for it: women showed less symptom improvement when treated for N&V with anti-emetic (e.g., 5-HT3-antagonistic) drugs (15). It has been postulated that polymorphisms of genes regulating the serotoninergic system may be responsible for the reduced effectiveness of anti-emetic medication, but the data are so far inconclusive (9,26,28), and a strong association of therapy effectiveness with gender has not been demonstrated.

Higher susceptibility to motion and motion-induced N&V is well established in Asian subjects, as compared with Caucasians or people of African origin. This holds true for experimentally-induced motion or pseudo-motion (24,25) and also for clinical conditions with increased risk of N&V, such as with chemotherapy in cancer patients (27) or invasive medical procedures (17). However, N&V associated with migraine seems to be lower in Asians as compared with Americans (26). Asian hypersusceptibility to motion sickness has been linked to genetic traits (16), but the data are so far inconclusive. Whether gender differences in motion sickness susceptibility as discussed above are maintained in the Asian population is so far unknown.

Motion sickness susceptibility can easily be tested in healthy volunteers using simple experimental paradigms, such as by inducing a visual-vestibular conflict with head movements during yaw motion in a conventional rotation chair, or by pseudorotation (circular vec-

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tion) in a rotation drum (19,21). Depending on experimental conditions (e.g., speed of rotation, orientation of the body axis, control of the visual field, etc.) a variable percentage of volunteers will report symptoms of N&V. Motion sickness susceptibility has also been tested using a paper-pencil test that asks for previous experience with symptoms of N&V during various everyday-life situations (driving a car, being on a boat) both during childhood and as adult. Such a test, the Motion Sickness Susceptibility Questionnaire (MSSQ), was developed and validated by Golding (6). This instrument was tested for different experimental and clinical paradigms, such as N&V induced by chemotherapy. However, gender and racial contributions to motion sickness susceptibility have not been evaluated so far with this instrument, and correlations between MSSQ scores and N&V during experimental and clinical conditions ranged between $r = 0.30$ and $r = 0.45$ (6), which are rather low for the prediction of individual behaviors.

The purpose of the present study, therefore, was two-fold: to test whether motion sickness susceptibility as determined by the MSSQ correlates with behavioral (i.e., RT) and subjective measures (i.e., SR), and to test whether and how ethnic origin and gender effects are reflected in these measures.

METHODS

Between 2001 and 2004, 4 cohorts with a total of $n = 227$ healthy male and female volunteers were recruited by one of the authors (S. Kellermann) from the student population of the University of Düsseldorf, Germany, through advertisement over the internet and on billboards. These volunteers were predominantly of European origin and are labeled "Caucasian" subsequently. In addition, 82 male and female subjects of Asian origin were recruited by another of the authors (F. Pan, who is of Chinese origin) among students in Düsseldorf and at other universities in near proximity. All these subjects were born in China and had two Chinese parents; they are subsequently labeled "Chinese."

For both the Caucasian and the Chinese samples the same recruitment text was used, except for the language. Both recruiters were women. All samples were recruited for the same purpose: the screening for susceptibility to motion sickness of potential subjects for Pavlovian conditioning and other learning studies (e.g., 10,11). Whether high or low susceptible subjects were preferred was not disclosed to the students until after termination of the screening. The Human Subject Ethical Committee of the Düsseldorf University Medical School approved the experimental protocol prior to the study, and all subjects gave written informed consent prior to participation.

All investigations were performed in the morning between 08:00 and 12:00. Subjects were instructed to fast for 12 h prior to arrival, but could drink non-caloric drinks (e.g., herbal tea) ad libitum. Blood glucose sticks were used to control for compliance to the fasting instructions.

Subjects seated in a conventional rotation chair were rotated around the yaw axis at a constant speed of $120° \cdot s^{-1}$ with their eyes closed, and for 5×1 min with 1-min interruptions. They were instructed by audiotape to move their heads up and down every 6 s with a pitch of approximately 90°. Subjects could terminate each rotation sequence on request but were asked to continue after a break of 1 min; the tolerated rotation times were added to produce a total RT time (in seconds). Subjects were also classified in five "rotation classes," depending on their RT, by subdividing the total rotation time possible (300 s) in five equal classes for non-parametric statistical comparisons. Prior to rotation, usually during recruitment, subjects filled out the MSSQ, a published and validated instrument (6) that had been translated from English into German as well as into Chinese with re-translation into English by different and experienced bilingual experts to ensure validity. Both the German and the Chinese version were, so far as we know, used for the first time here.

The MSSQ asks for previous experiences with motion sickness in different everyday-life situations (e.g., riding in a car, on a merry-go-round, on a boat) during childhood (subscale A; MSSQ-A) and during adult life (subscale B; MSSQ-B), and scores each of these between 1 and 5. A sum score for MSSQ-A and MSSQ-B was computed as well as a total score (A + B; MSSQ-AB). The normative data (mean $\pm$ SD) as given by Golding (6) were 28.8 ± 23.3 for the MSSQ-A, 16.7 ± 17.5 for MSSQ-B, and 45.5 ± 37.6 for the MSSQ-AB. Women's scores were higher (51.8 ± 42.0) than men's scores (38.5 ± 29.6) for the MSSQ-AB.

Rating of nausea-associated symptoms (SR) was performed on a 7-item symptom scale (vertigo, headache, nausea, urge to vomit, tiredness, sweating, stomach awareness) between 0 (not present) and 5 (very strong), which had been used previously (11,12). SR ratings were made at the beginning, approximately 10 min prior to rotation (SR-10), and immediately after the end (SR0) of each rotation, as well as 15 and 30 min later (SR15, SR30). A total symptom score was computed as the sum of all ratings at each time point (SR-10, SR0, SR15, SR30). The maximal symptom rating achieved during the five rotations was used as SR0.

Data were compared using a 2×2 MANOVA with the two between factors gender (male, female) and ethnic origin (called "origin" subsequently; Caucasian, Chinese) for all groups of dependent variables (MSSQ-A, MSSQ-B, MSSQ-AB; RT; SR-10, SR0, SR15, SR30). Post hoc *t*-tests were used to explore significant MANOVA differences. Correlations between different groups of measurements were assessed by Pearson's correlation coefficient, and non-parametric testing of the distribution of rotation classes used the Chi-square test. Significance level was set to 0.05 for all tests.

RESULTS

All four cohorts of Caucasian volunteers were comparable with respect to age (between 19 and 41 yr). Cohorts 1 and 2 ($n = 50$ and $n = 40$) had an equal number of men and women. The gender distribution in samples 3 and 4 ($n = 73$, and $n = 64$, respectively) was chosen to be in favor of women to ensure enough female subjects for subsequent conditioning experiments which were intended to include only women (see

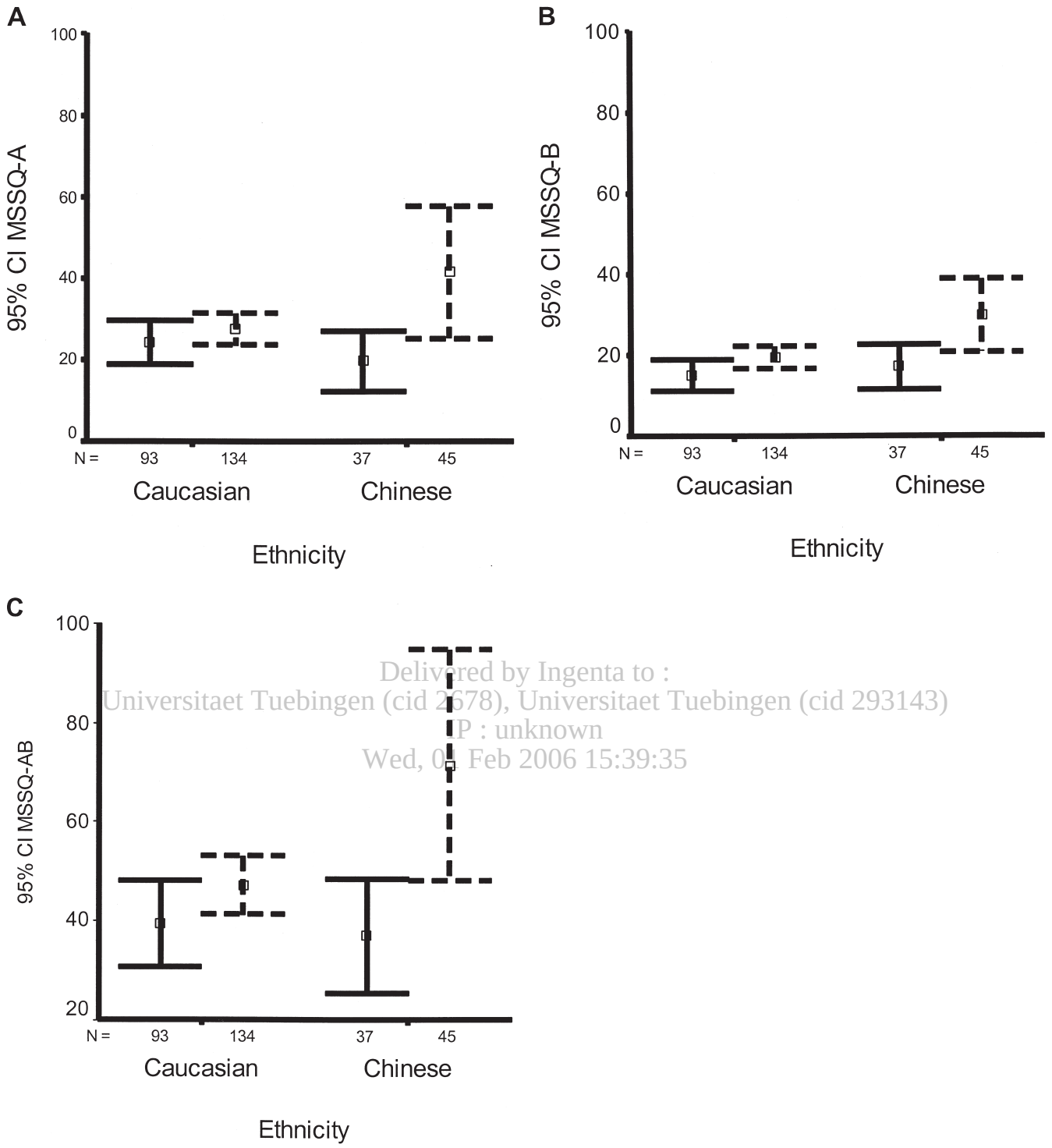

Fig. 1. A) Motion Sickness Susceptibility A (MSSQ-A; child) score; B) MSSQ-B (adults) score; C) MSSQ-AB (combined A+B) score (mean, 95% CI) for Caucasian and Chinese men (solid lines) and women (dotted lines).

11). Overall, the sample included 93 men and 134 women. They were also comparable for other variables such as the height (mean: 173.8 ± 8.4 cm), weight (67.4 ± 11.4 kg), and BMI (22.2 ± 2.8). Consequently, these cohorts were merged into one group ("Caucasians") for the comparison with the Chinese volunteers (26.7 ± 4.5 yr; 37:45, men:women).

MSSQ scores were differentially affected by the factor of origin: the child score (MSSQ-A) was significantly different between Caucasians and Chinese (main effect of origin; $F = 6.05$, $p = 0.014$), although the effect on the adult score (MSSQ-B) was not significant, and the combined score (MSSQ-AB) did not quite reach significance levels ($F = 3.37$, $p = 0.067$). Gender significantly affected all three scores independent of ethnicity, but was strongest for the combined (MSSQ-AB) score (main ef-

TABLE I. INTERCORRELATIONS BETWEEN VARIOUS VARIABLES OF THE ANALYSIS (TOTAL NUMBER OF SUBJECTS, N = 309). LOWER LEFT PART LISTS THE R VALUES (PEARSON'S CORRELATION COEFFICIENT), UPPER RIGHT HALF THE RESPECTIVE SIGNIFICANCE LEVELS (***p < 0.001, n.s.: NOT SIGNIFICANT)

	MSSQ-A	MSSQ-B	MSSQ-AB	RT (s)	SR-10	SR0
MSSQ-A	—	***	***	***	***	n.s.
MSSQ-B	0.69	—	***	***	***	n.s.
MSSQ-AB	0.95	0.88	—	***	***	n.s.
RT (s)	−0.24	−0.30	−0.28	—	***	***
SR-10	0.33	0.33	0.36	0.28	—	***
SR0	0.07	0.11	0.09	−0.41	0.28	—

MSSQ-A: Motion Sickness Susceptibility Questionnaire score A for childhood; MSSQ-B: Motion Sickness Susceptibility Questionnaire score B for adulthood; MSSQ-AB: combined MSSQ-A and MSSQ-B score; RT: Rotation tolerance; SR-10: Maximal symptom rating 10 min prior to rotation; SR0: maximal symptom rating during rotation.

fect of gender: $F = 12.73$, $p < 0.001$). A significant interaction between ethnic origin and gender was found for the child (MSSQ-A) and the combined (MSSQ-AB) score, but was strongest for the MSSQ-A score (Origin × Gender: $F = 5.64$, $p = 0.0180$). The scores were particularly high for Chinese women (post hoc *t*-test for the A and B scores: $t = 2.44$, $p = 0.016$ and $t = 2.95$, $p = 0.004$, respectively), but not significantly different for both groups in men (**Fig. 1**).

RT was significantly less in Chinese volunteers (111 ± 7 s) than in Caucasians (63 ± 6 s), but was not affected by gender (main effect of factor "origin": $F = 24.84$, $p < 0.001$). Rotation significantly increased SR0 independent of origin and gender (main effect of rotation: $F = 752.9$, $p < 0.0001$). At SR15 and SR30, ratings were not different from the baseline measurement at SR-10. Motion sickness susceptibility on the MSSQ, SR0, and RT significantly correlated with each other (**Table I**), although the correlations were rather low and ranged between $r = -0.40$ to $r = 0.36$ (all significant) except for the higher intercorrelations between the various MSSQ scores.

This pattern of results was not different when only Caucasian volunteers (n = 227) were taken into consideration. Correlations were also similar (but weaker) when only the data from Chinese subjects (n = 82) were taken. When the rotation tolerance classes were used to classify the MSSQ scores, a high predictive value of the MSSQ became evident for rotation tolerance, although separate for the genders (**Fig. 2**), particularly for the RT classes 1 (RT ≤ 60 s) and 5 (RT > 240 s), which represented 31% and 16.2%, respectively, of the total sample. The separation was better for the MSSQ-B and the combined MSSQ-AB score than for the MSSQ-A (child) score.

DISCUSSION

The MSSQ is an instrument that allows identification of individuals likely to develop symptoms of N&V following different emetogenic stimuli (body rotation, cancer therapy, etc.), and gender effects have been obtained with this instrument (6). As we show here, the MSSQ adult scale (B), in particular, needs to be adjusted for gender to allow for these differences, since they are significantly higher in women as compared with men, for subjects with extremely high susceptibility as well as for those with low susceptibility. Overall, the results described here are well in agreement with the normative values given by Golding (6).

As we show here for the first time, the MSSQ scales also have to be adjusted for potential racial differences, at least for Asian subjects. Some of the differential findings may be explained by translational problems induced by the test instruments; although the tests were translated and re-translated, they have not been properly validated for a non-English population. It is also evident from our data that the MSSQ ratings given by the Chinese volunteers did not reflect their higher susceptibility during the subsequent test. This may indicate that Chinese are in general less aware of their susceptibility to motion and, therefore, underestimate its consequences. It may also be that Chinese do experience less nausea-evoking symptoms in their everyday life. This could be tested with a single-item analysis of the MSSQ that lists a variety of potential nauseogenic situations; it would need to be shown that Chinese report more "zero" answers, indicating that they were never exposed to these situations, compared to Caucasians. The alternative explanation, that they may report fewer symptoms for cultural or social reasons, cannot be excluded. It would be necessary to test this in a setting with both Chinese and non-Chinese male and female experimenters.

We speculate that both a biological and a psychological mechanism may be responsible for gender differences in nausea symptom reports. Gender differences in nausea reports have also been found in human learning experiments: we recently observed significant effects of gender on nausea symptoms using a motion sickness paradigm and learning procedures such as habituation (22), latent inhibition (12), and overshadowing. In all these experiments, women were more prone to be conditioned and also profited more from countermeasures based on conditioning to inhibit nausea symptoms; in general, however, the direction of response was similar between the genders. The reason for increased learning capacity in relation to nausea symptoms in women as compared with men remains unclear.

In contrast to subjective symptoms, gender differences in biological markers of nausea showed distinctly different directions of response in men and women during learning experiments; e.g., although endocrine responses generally habituated with repetitive rotation, the free cortisol response in men did not, and proinflammatory cytokine production showed a gender-specific response pattern with initial increases in men and decreases in women (22). Response patterns of glucocorticoid sensitivity also changed over time: in the first session, sensitivity increased only in men, but in the last session, sensitivity decreased in all subjects. Similarly, distinctively different response patterns for cortisol and TNF-a were seen between the genders in a recent experiment on overshadowing.

The data from the present study only in part confirm

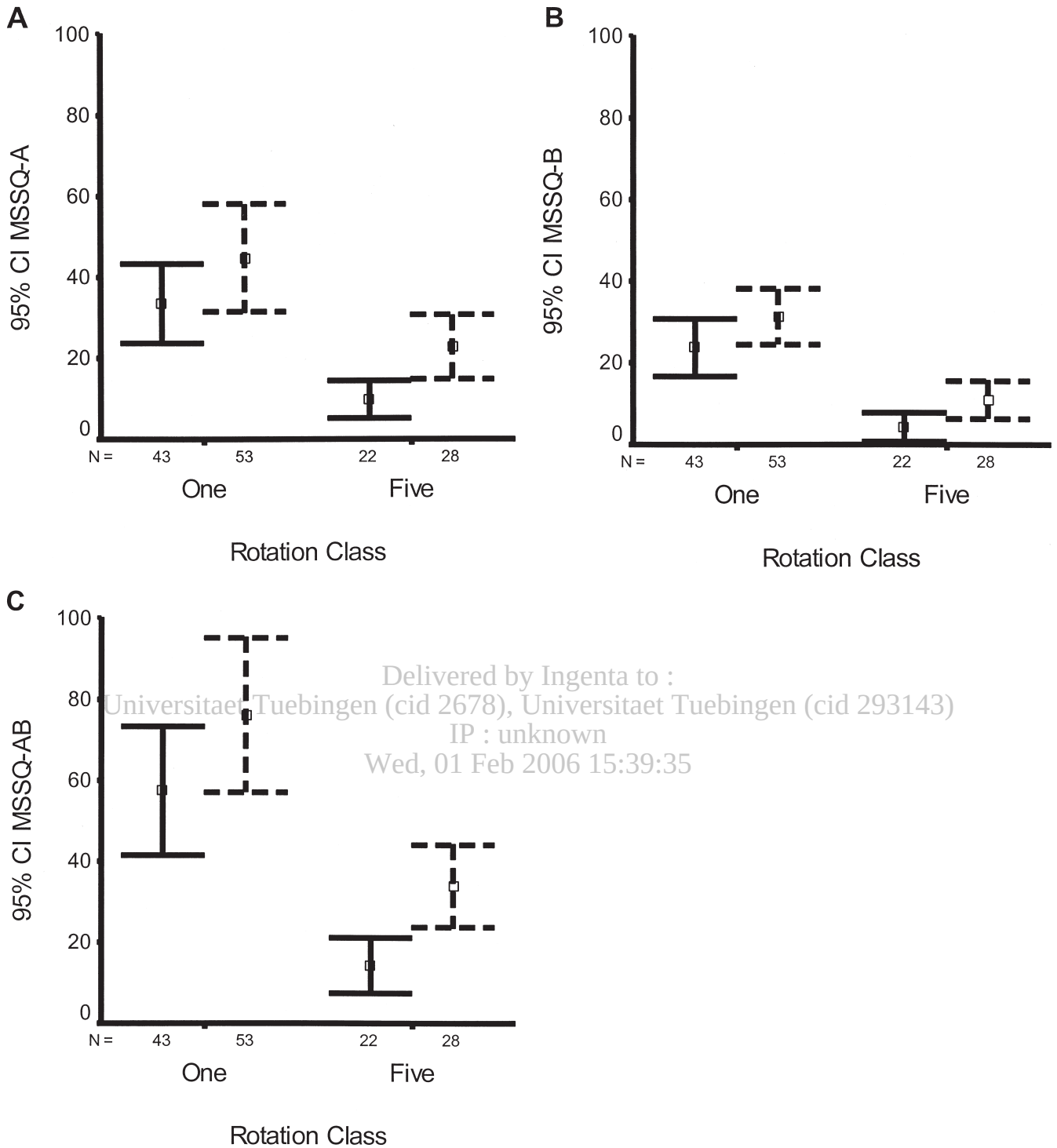

Fig. 2. A) Motion Sickness Susceptibility A (MSSQ-A; child) score; B) MSSQ-B (adults) score; C) MSSQ-AB (combined A+B) score (mean, 95% CI) for men (solid lines) and women (dotted lines) in rotation classes 1 (< 60 s rotation tolerance) and 5 (> 240 s).

previous findings: women did not show lower tolerance to rotation, as we had expected, but tolerated rotation to the same degree as their male counterparts in both Chinese and Caucasian volunteers. In contrast to previous reports, however, women did not report higher subjective symptoms (SR) than men when acutely exposed to a nauseogenic body rotation. Instead, they scored significantly higher on the MSSQ asking for previous experience with N&V under various everyday-life situations during childhood and adult life; this agrees with one other study in the literature (20). It remains to be clarified whether a positive motion sickness history in women is the responsible intra-individual factor contributing to increased N&V symptom reports under clinical conditions as discussed above.

Differences in relation to ethnic origin are well established for motion sickness susceptibility, and several reports have shown that Chinese subjects especially are significantly more susceptible than Caucasians to body rotation and/or to visual-vestibular conflict during pseudo-rotation (24,29). This has led to the conclusion that genetic influences may co-determine individual responsiveness to such stimuli (25), but such statements remained rather vague until recently when genetic screening for candidate genes in the human genome became available. A preliminary report has named the α (2A)-AR gene on chromosome 10 (16), but the data lack appropriate controls (only one English, but 13 Asian subject were tested). Others have linked the incidence and severity of N&V to the serotonin-transporter gene (SERT) regulating serotonin reuptake, and to other polymorphisms of the serotonergic system (9,27). However, these reports have not been able so far to reliably explain or predict N&V responses under clinical conditions, e.g., in cancer therapy. Whether susceptibility to developing N&V during experimental motion is linked to the well-established Asian hypersensitivity to alcohol and its genetic determination through polymorphisms of the alcohol metabolizing ADH enzyme system (2) has not been tested, but may be of interest in future research. Finally, linking motion sickness susceptibility to other forms of sensory hypersensitivity, e.g., to chemical, olfactory, and gustatory stimuli as described for hyperemesis gravidarum (7), or to genetic traits in functional bowel disorders (18), may speed up the search for further candidate genes, which may be able to explain these findings in the future.

The present study has some limitations that need to be acknowledged. One is the fact that variability between experimenters who were of different ethnic background may have been confounded with ethnic differences in motion sickness susceptibility, and with potential response biases that may have occurred as the consequence of either of these factors; this may be overcome by appropriate experimental variation of these factors in the future. A second limitation may arise from language differences in the questionnaires and rating instruments used (MSSQ, SR). This may require explicit cultural validation rather than mere translation of instruments. Finally, we tested susceptibility only to nauseogenic body rotation in a rotation chair, and not to other stimuli such as pseudo-motion (vection) in a rotation drum. This needs to be done to support the general conclusions drawn from the present data.

In summary, motion sickness and motion sickness susceptibility are strongly influenced by gender and ethnic origin, but in a differential fashion. This will require adjustment of tests for both conditions. However, when these factors are adequately controlled for, the MSSQ is a reliable paper-pencil screening instrument for future research. Differences in motion sickness susceptibility may require genetic screening tools to identify the relevant candidate genes.

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