MAJOR ARTICLE

Sex and Gender Differences in Travel-Associated Disease

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Background. No systematic studies exist on sex and gender differences across a broad range of travel-associated diseases.

Methods. Travel and tropical medicine GeoSentinel clinics worldwide contributed prospective, standardized data on 58,908 patients with travel-associated illness to a central database from 1 March 1997 through 31 October 2007. We evaluated sex and gender differences in health outcomes and in demographic characteristics. Statistical significance for crude analysis of dichotomous variables was determined using χ^2 tests with calculation of odds ratios (ORs) and 95% confidence intervals (CIs). The main outcome measure was proportionate morbidity of specific diagnoses in men and women. The analyses were adjusted for age, travel duration, pretravel encounter, reason for travel, and geographical region visited.

Results. We found statistically significant ($P < .001$) differences in morbidity by sex. Women are proportionately more likely than men to present with acute diarrhea (OR, 1.13; 95% CI, 1.09–1.38), chronic diarrhea (OR, 1.28; 95% CI, 1.19–1.37), irritable bowel syndrome (OR, 1.39; 95% CI, 1.24–1.57), upper respiratory tract infection (OR, 1.23; 95% CI, 1.14–1.33); urinary tract infection (OR, 4.01; 95% CI, 3.34–4.71), psychological stressors (OR, 1.3; 95% CI, 1.14–1.48), oral and dental conditions, or adverse reactions to medication. Women are proportionately less likely to have febrile illnesses (OR, 0.15; 95% CI, 0.10–0.21); vector-borne diseases, such as malaria (OR, 0.46; 95% CI, 0.41–0.51), leishmaniasis, or rickettsioses (OR, 0.57; 95% CI, 0.43–0.74); sexually transmitted infections (OR, 0.68; 95% CI 0.58–0.81); viral hepatitis (OR, 0.34; 95% CI, 0.21–0.54); or noninfectious problems, including cardiovascular disease, acute mountain sickness, and frostbite. Women are statistically significantly more likely to obtain pretravel advice (OR, 1.28; 95% CI, 1.23–1.32), and ill female travelers are less likely than ill male travelers to be hospitalized (OR, 0.45; 95% CI, 0.42–0.49).

Conclusions. Men and women present with different profiles of travel-related morbidity. Preventive travel medicine and future travel medicine research need to address gender-specific intervention strategies and differential susceptibility to disease.

A total of 903 million international tourist arrivals were recorded in 2007 [1]. In general, more men than women travel; 53% of >30 million US outbound travelers are male. Men predominate in business travel (accounting for 74% of business travelers) [2]. Travel is associated with an increased risk of health problems, and although most illnesses are self-limiting, ~8% of travelers will require medical attention [3]. Most studies of ill travelers provide few detailed data on sex and gender. In the online medical literature databases for the period 1983–2008, there are no systematic studies

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on sex differences in travelers across a broad range of health risks, yet being male or female is an important human variable that affects health and illness. Differences between the sexes in the incidence and severity of infection will be related to genetic and physiological constitutions [4] but also to differences in exposures, attractiveness to vectors, routes of pathogen entry, processing of pathogens and cellular responses, participation in high-risk activities, and use of preventive strategies. In terms of travel-associated morbidity, we sought to determine whether there are sex and gender differences in travel characteristics, presenting symptoms, and diagnoses and whether potentially gender-associated behavioral patterns could be identified. Our study confirmed sex-associated symptoms and diagnoses and showed differing behavioral patterns in men and women in the context of travel-associated illness.

METHODS

We analyzed data from the GeoSentinel network's 44 sites [5] from 1 March 1997 through 31 October 2007 according to demographic characteristics and travel related morbidity. A GeoSentinel site is a clinic specializing in travel or tropical medicine that contributes clinician-based data on ill travelers seen during or after travel.

Inclusion criteria. To be eligible, patients must have crossed an international border ⩽10 years before presentation and must have sought medical advice for a presumed travel-related illness. Only final, confirmed, and probable diagnoses were considered, and >1 diagnosis per patient was possible. Final diagnoses were assigned by a physician.

Data were collected according to a standardized, anonymous questionnaire and entered into a Structured Query Language database. The questionnaire comprises demographic data (age, sex, country of birth, country of residence, current citizenship), travel history during the previous 5 years, inpatient or outpatient status, major clinical symptom (>1 symptom per patient is possible), pretravel encounter for travel health advice, reason for most recent travel, and patient classification. Included in the analysis were those individuals who traveled for tourism, to visit friends and relatives, for business, for research or education, for military purposes, and for missionary or volunteer work. Those individuals who traveled for immigration were excluded.

Diagnostic categories. Final diagnoses were assigned a diagnostic code from a standardized list of >500 diagnoses, which were also categorized into 21 broad syndrome groups. Summary diagnosis "respiratory tract infections" includes upper and lower respiratory infections; "malaria" includes infections with all malaria species; "diarrhea" includes acute diarrhea of parasitic, viral, bacterial, or unknown origin; "hepatitis" includes chronic or acute viral hepatitis; "viral syndrome" includes nonspecific viral symptoms; "AIDS/HIV/STI" includes asymptomatic human immunodeficiency virus (HIV) infection, acute HIV infection, AIDS, gonorrhea, syphilis, and other sexually transmitted infections (STIs). Syndrome groups, such as "dermatologic disorder," were defined as previously described [6].

Statistical analysis. The data were analyzed using SPSS software, version 15 (SPSS). Statistical significance for crude analysis of dichotomous variables was determined using χ^2 tests with calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analysis with logistic regression was performed to adjust data for factors that were statistically significant on univariate testing. The logistic regression results for female versus male individuals were adjusted for age, travel duration (>30 days vs <30 days), whether the individual was seen during or after travel, pretravel encounter, reason for travel, and geographical region visited. Proportionate morbidity was calculated as the number of patients with a specific or a summary diagnosis as a proportion of all men or women, respectively, expressed per 1000 patients.

RESULTS

There were a total of 58,908 travelers included in the analysis; 50.3% were female, and 49.7% were male.

Demographic characteristics. Female travelers were more likely than male travelers to be younger, have a shorter duration of travel, be tourists, have pretravel health advice, and present during travel and were less likely than male travelers to be treated as an in-patient (Table 1). There was no statistically significant difference between proportions of men and women who reported high-risk travel (eg, backpacking or off-track travel).

Diagnosis. Women had a higher proportionate morbidity for all types of diarrhea and respiratory morbidity (except pneumonia). Men, however, had a significantly higher proportionate morbidity for all febrile illnesses, including the vector-transmitted diseases, such as malaria, dengue, rickettsioses, and leishmaniasis. Male travelers had a higher risk of acute hepatitis A, chronic viral hepatitis, and any STI, whereas women were more susceptible to urinary tract infections. With regard to noncommunicable health risks, there were significant differences between the sexes. Women were more likely to present with psychological stressors, adverse reactions to medications, and oral and dental conditions, whereas men presented with an excess of acute mountain sickness and frost bite (Table 2 and Figure 1).

DISCUSSION

Differing behavior, cognition, metabolism, responses to medication or vaccines, and susceptibility to infectious disease lead to distinct profiles of travel-associated morbidity for men and women. These differences are related to sex, gender, or both.

Table 1. Demographic Characteristics of Ill Travelers Presenting During and After Travel at GeoSentinel Clinics Worldwide

Variable	Female patients (n = 29,643)	Male patients (n = 29,265)	P	OR[a] (95% CI)
Percentage of total patients	50.3	49.7		
Age				
Mean years	34.4	35.9	<.001	
⩽30 years old	14,061 (53.9)	12,014 (46.1)	<.001	1.30 (1.25–1.33)
Reason for travel				
Business	6195 (20.9)	8206 (28.0)	<.001	0.68 (0.65–0.70)
Health	461 (1.6)	419 (1.4)	.220	1.09 (0.95–1.24)
Military	4 (<0.1)	34 (0.1)	<.001	0.12 (0.04–0.33)
Missionary	3421 (11.5)	2845 (9.7)	<.001	1.21 (1.15–1.28)
Student	545 (1.8)	403 (1.4)	<.001	1.34 (1.18–1.53)
Tourism	19,017 (64.2)	17,358 (59.3)	<.001	1.23 (1.19–1.27)
Travel risk level				
Expatriate	6487 (21.9)	7107 (24.3)	<.001	0.87 (0.84–0.91)
Prearranged or organized travel	2435 (8.2)	3787 (12.9)	<.001	0.60 (0.57–0.64)
Risk travel	1088 (3.7)	1102 (3.8)	.540	0.97 (0.89–1.06)
Ill and presenting during travel	12,952 (43.7)	12,153 (41.5)	<.001	1.09 (1.06–1.13)
In-patient	1338 (4.6)	2762 (9.5)	<.001	0.45 (0.42–0.49)
Pretravel encounter	17,151 (68.2)	15,425 (62.7)	<.001	1.28 (1.23–1.32)
Duration of travel >30 days	9894 (42.4)	9649 (42.4)	.970	1.00 (0.96–1.04)
Region of travel				
Pacific	942 (3.2)	1041 (3.6)	.100	0.89 (0.81–0.97)
Latin America	3915 (13.2)	3913 (13.4)	.600	0.99 (0.94–1.03)
Europe	3625 (12.2)	3343 (11.4)	.002	1.08 (1.03–1.14)
North America	1356 (4.6)	1261 (4.3)	.120	1.07 (0.98–1.15)
Africa	5462 (18.4)	5652 (19.3)	.006	0.94 (0.91–0.98)
Asia	14921 (50.3)	14509 (49.6)	.070	1.03 (1.0–1.07)

NOTE. Data are no. (%) of patients, unless otherwise indicated. The mean time to presentation did not differ significantly between men and women. The following data were missing: age, 207 patients; risk level qualifier, 36,902 patients; in-patient, 687 patients; pretravel encounter, 9131 patients; duration of travel, 12,833 patients. CI, confidence interval; OR, odds ratio.

[a] All ORs are for traveler being female versus male.

Sex is biologically determined (the sexual genotype is XX in the female and XY in the male), but gender relates to a person's self-representation as male or female and to the manner in which social institutions influence that person. Gender is shaped by environment and experience [7]. Our study is, to our knowledge, the first to explore the spectrum of travel-related illness in terms of sex and gender, and with the use standard analyses, we found statistically significant differences in the spectrum of travel-associated illness in men and women.

We found that ill women who presented to travel clinics were significantly more likely to have sought pretravel advice than were their male counterparts (OR, 1.28; 95% CI, 1.23–1.32). Other studies have also shown that female sex is independently associated with receiving pretravel health information [8] and also with increased concern about travel stressors [9]. In addition, as shown by their predominance in the GeoSentinel collective, women, compared with men, present more often after travel with presumed travel-associated morbidity, but either their conditions are more benign or medical services treat men differently, because men are more likely than women to be treated as in-patients or referred to hospitals [9, 10]. One study of travel-related hospitalizations [10] found that 71% of hospitalizations were of male patients. We found no significant differences in the numbers of deaths recorded for men and women in our analysis, but studies on travel-related deaths [11, 12] and road traffic accidents [13] show that such events predominantly involve men.

Our study showed that women who present to travel clinics are more likely than men to report an adverse event related to medication (OR, 1.39; 95% CI, 1.11–1.73), and this has been borne out by the literature, particularly regarding the tolerability of medications used for malaria prophylaxis (specifically, mefloquine, for which several studies have shown significantly poorer tolerability among women than among men) [14–16].

Table 2. Comparison of Diagnoses in Ill Female and Male Travelers Who Presented to GeoSentinel Clinics Worldwide

Diagnoses in travelers	No. (%) of patients, by sex		OR (95% CI)
	Female (n = 29,643)	Male (n = 29,265)	
Diarrhea			
Acute diarrhea	7290 (24.6)	6322 (21.6)	1.13 (1.09–1.38)
Acute bacterial diarrhea	3681 (12.4)	3257 (11.1)	1.06 (1.0–1.11)
Acute parasitic diarrhea	1712 (5.8)	1485 (5.1)	1.14 (1.06–1.23)
Acute unspecific diarrhea	2039 (6.9)	1713 (5.9)	1.18 (1.10–1.26)
Chronic diarrhea	1922 (6.5)	1543 (5.3)	1.28 (1.19–1.37)
Irritable bowel syndrome	679 (2.3)	502 (1.7)	1.39 (1.24–1.57)
Respiratory morbidity			
Acute respiratory infection	3437 (11.6)	3122 (10.7)	1.08 (1.03–1.14)
Upper respiratory tract infection	1504 (5.1)	1188 (4.1)	1.23 (1.14–1.33)
Pneumonia	215 (0.7)	391 (1.3)	0.53 (0.46–0.64)
Fever, vector borne Infection			
Febrile systemic illness	3357 (11.3)	5082 (17.4)	0.64 (0.61–0.67)
Malaria	455 (1.5)	1004 (3.4)	0.46 (0.41–0.51)
Dengue	514 (1.7)	915 (3.1)	0.63 (0.56–0.71)
Rickettsia	81 (0.3)	150 (0.5)	0.57 (0.43–0.75)
Leishmania	84 (0.3)	150 (0.5)	0.57 (0.43–0.74)
Febrile exanthem	34 (0.1)	304 (1.0)	0.15 (0.10–0.21)
Genitourinary			
Urinary tract infection	744 (2.5)	188 (0.6)	4.01 (3.34–4.71)
STI (AIDS, HIV infection, syphilis, gonorrhea)	239 (0.8)	362 (1.2)	0.68 (0.58–0.81)
Acute HIV infection	7 (<.01)	38 (1.0)	0.20 (0.09–0.44)
Other condition			
Frostbite	21 (0.1)	145 (0.5)	0.14 (0.09–0.22)
Mountain sickness	298 (1.0)	525 (1.8)	0.54 (0.47–0.63)
Psychological problems	527 (1.8)	403 (1.4)	1.30 (1.14–1.48)
Anxiety/fatigue	877 (3.0)	696 (2.4)	1.27 (1.15–1.41)
Cardiovascular disease	211 (0.7)	411 (1.4)	0.56 (0.47–0.66)

NOTE. A total of 44 GeoSentinel sites on 6 continents contributed data to the central database. $P < .001$ for all variables, adjusted for age, travel duration (>30 days vs <30 days), whether the individuals was seen during or after travel, pretravel encounter, reason for travel, and geographical region visited. CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; STI, sexually transmitted infection.

Men were proportionally more likely to have febrile systemic illness (OR, 1.6), and a recent study on fever in travelers showed that 58% of ill travelers who presented with fever were male and that 71% of those who present with fever and malaria are male [17]. Several studies have shown that men are more likely than women to acquire malaria [18, 19], leishmaniasis [20], and West Nile virus infection [21] than are women. One study of leptospirosis involving German travelers found that male sex was associated with a higher severity of clinical disease not related to differences in exposure risks or health-seeking behavior [4]. Malaria infection in men is also more severe, with men being more likely than women to die from malaria [10, 22, 23]. Male travelers are also at greater risk of infection with multiple clones of *Plasmodium falciparum* [24]. Female mosquitoes, including the malaria-transmitting *Anopheles* and the dengue-transmitting *Aedes (Stegomia)*) need blood for the development of their eggs, and their host-seeking behavior has been perfected over centuries of evolution. There are several reasons why men may be more attractive hosts than women for mosquitoes. It is known that mosquitoes identify their hosts by use of a variety of cues, the most important being olfactory. Identified olfactory cues are carbon dioxide, sweat, and volatile skin products, and men produce more of these mosquito attractants than do women. This has been suggested as a biological factor that increases male susceptibility to mosquito-borne infection. Furthermore, repellents are water-soluble, and individuals who sweat profusely (mainly men) will need to reapply repellents frequently. Other analyses have suggested that

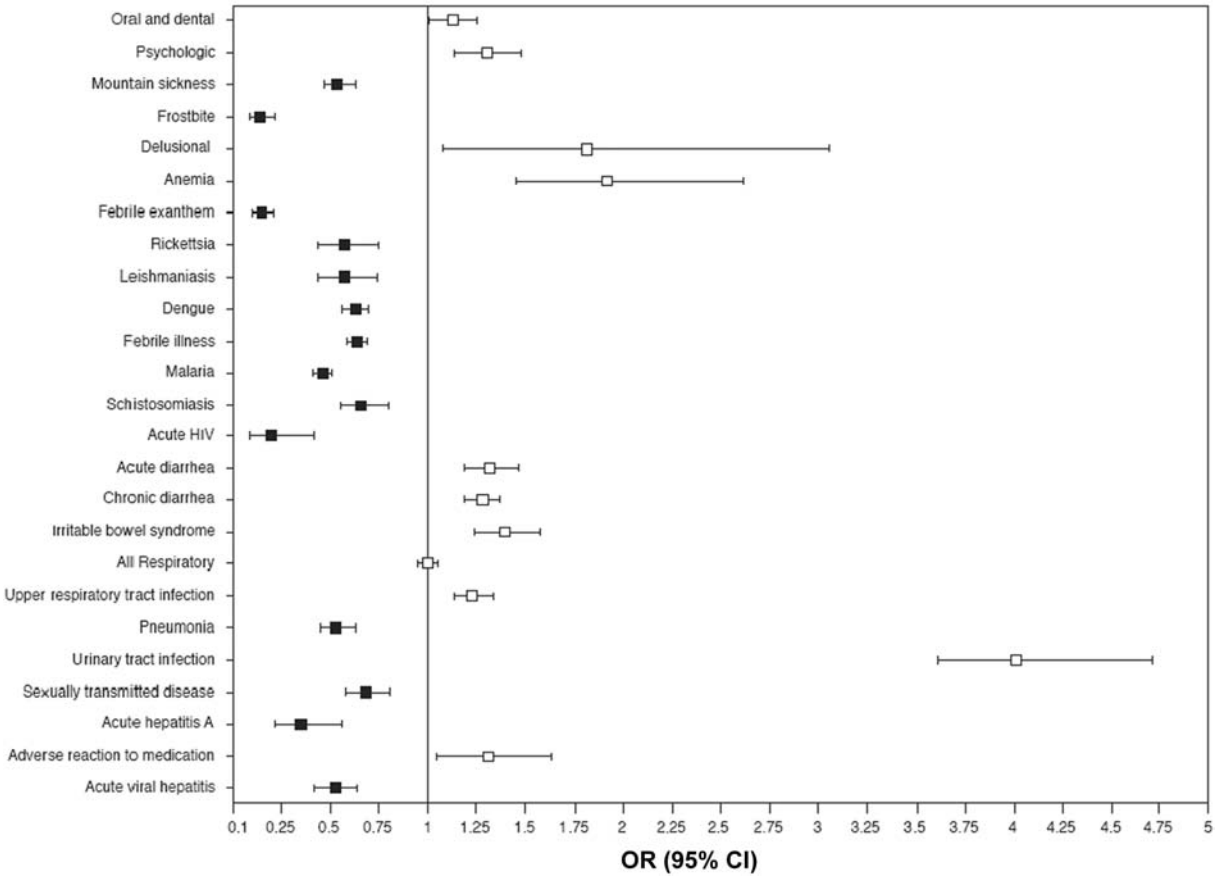

Figure 1. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for diagnoses profiles for female and male travelers. ORs (for female versus male travelers) are squares (*filled squares* show illnesses more likely to occur in men, and *open squares* show illnesses more likely to occur in women), and 95% CIs are lines; diagnoses profiles in female and male travelers are adjusted for age, travel duration, region of travel, reason for travel, pretravel encounter, and whether the individual was seen at a GeoSentinel site during or after travel. Delusional, delusional parasitosis; HIV, human immunodeficiency virus infection.

male predominance in travelers' malaria is attributable to risk-taking behavior [10] or to poorer adherence to personal protection measures against mosquito bites and chemoprophylactic medication. With regard to diarrhea and gastrointestinal illness, there is some literature that shows that female sex is a predictor of diarrhea and gastrointestinal illness [25, 26]. However, other epidemiological studies [27] and a recent retrospective survey found no association between sex and diarrhea [28], perhaps because of the small sample size included in that study (n = 108). It is unclear whether women practice travel behavior that increases the risk of acquiring gastrointestinal pathogens or whether they are more likely than men to seek medical help for gastrointestinal problems. *Salmonella* Typhi infections have been reported to occur more frequently among men than among women [29, 30], but our study found only a small, nonsignificant excess of *Salmonella* Typhi infection among male individuals (P = .100). A recent study of amebic dysentery prompted by the observation that men are >7 times more likely to develop amebic liver abscess or amebic dysentery than are women found biological differences: serum from women was significantly more effective in killing *Entamoeba histolytic* trophozoites than was serum from men [31].

With regard to STIs, several studies have shown that male travelers are more likely to have casual sex than are female travelers [32–34]. A British study found that 13.9% of men and 7.1% of women have new sexual partners while overseas [34]. Among respondents who were younger (aged 16–24 years) and never married, the proportions were significantly higher (23% and 17%, respectively). Clearly, sexual health promotion needs more attention from pretravel health advisors.

GeoSentinel collects data on a large sentinel sample of ill travelers and uses proportionate morbidity as an indicator of likely diagnoses occurring in travelers. The strength of the GeoSentinel database lies in the clinically verified data on a large number of travelers and diseases. Our study, however, has some limitations. Chiefly, these are that only a proportional sample of cases of disease is captured and that the use of the proportionate morbidity ratio does not allow for the calculation

of absolute risk or true incidence rates of disease, because denominator data are not available. Many returned travelers, particularly those with mild or self-limiting conditions, are seen in nonspecialized, general practice. Some conditions with a short incubation period will be treated during travel, and individuals with those conditions may not present to the network clinics. GeoSentinel sites are usually located within academic centers, and many patients with imported illness that is neither mild nor self-limited but is suggestive of an exotic imported disease will present spontaneously or are referred by general practitioners. This does introduce some selection and reporting bias. However, this is not a key factor in the current analysis, because we are comparing proportionate morbidity of disease in men and women, and the selection bias will apply to both sexes.

A further study limitation is that the identified differences in morbidities between men and women could not clearly be attributed to sex (ie, biological) or gender (ie, cultural) factors. New research is indicated. Furthermore, we have few data on death and injury sustained by men and women, and injury is recognized as a major cause of morbidity among travelers.

Although it can be difficult to disentangle the effects of sex and gender on health risks, this study has found significant differences in travel-associated morbidity between men and women. Certain conditions, such as the predominance of urinary tract infection in women, can likely be explained by inherent differences in physiology and anatomy. However, higher proportional risks among men for febrile illnesses, vector-borne diseases, viral hepatitis, or sexually transmitted infections and the higher proportion of women who present with diarrhea, acute respiratory infection, oral or dental conditions, adverse events related to medication, or psychological problems warrant further investigation. Exploring these sex differences and the cultural influences that foster more-risky behavior among male individuals will open new avenues of research. Practical implications for preventive and therapeutic travel medicine practice are as follows: female travelers should be prepared to self-treat urinary tract infection and can be predicted to need more anti-diarrhea treatment. The pretravel advice should provide concise information on the tolerability of medication and how this may vary between the sexes, and dosage adjustments may be needed for women with low body weight. All travelers need advice on mosquito-transmitted infections, but men need to be particularly sensitized regarding adherence to mosquito bite prevention measures and the need for frequent application of repellents. Safe sex advice is a missing component in most pretravel practices, and our study suggests that male travelers, in particular, would benefit from greater preventive efforts. Our study has significant implications for travel medicine and can be used to prioritize prevention advice based on gender susceptibility to travel-related conditions.

GEOSENTINEL SURVEILLANCE NETWORK

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