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Establishment of Health Utility Indices for Post-Infectious Functional Gastrointestinal Disorders in Active Duty US Military

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Introduction. Knowledge of disease burden attributable to functional gastrointestinal disorders (FGD) in travelers is lacking, despite the high incidence of travelers' diarrhea (TD) associated with increased FGD risk. One tool for assessing the impact of disease on health-related quality of life is the health utility index (HUI), which values health states based on preferential health outcomes. Health utilities can be used as preference weights in the estimation of quality-adjusted life-years (QALYs).
Methods. Six months following travel to Egypt or Turkey, 120 US military personnel completed a survey on TD during deployment, health-related quality of life (SF-36), and the onset of functional bowel disorders (Rome II). Elements from the SF-36 were used to develop SF-6D values, which were combined with health state valuations to enable calculation of HUI scores for each subject. Mean index scores were compared across functional outcomes, specific symptoms, and demographic profiles.
Results. The presence of FGD significantly reduced index scores, with irritable bowel syndrome (IBS) and dyspepsia showing the greatest impact (−0.17 and −0.19, respectively) compared with those with no FGD ($p < 0.05$). Importantly, however, several individuals met multiple FGD outcome definitions. Additionally, a number of symptoms associated with abnormal bowel habits and abdominal pain were associated with reduced index scores regardless of outcome.
Conclusion. FGD are associated with significant morbidity as assessed by HUIs. Given the strong link between TD and FGD as well as the large number of travelers from the developed to the developing world, additional study is needed to further understand this association and efforts aimed at primary disease prevention are warranted.

Recent studies have highlighted the importance of the sequelae of infectious gastroenteritis caused by food-borne and waterborne pathogens.[1–5] Some of the most prevalent of these sequelae are the functional gastrointestinal disorders (FGD). While lacking a diagnostic test (though some have diagnostic definitions), these chronic conditions based on symptom-complex are often associated with physiological changes to the individual and are reported to be associated with significant morbidity and healthcare-related costs, though specific estimates of morbidity and costs in this population are limited.[6,7] The morbidity associated with these FGD is an area of ongoing effort to quantify the burden of these illnesses as post-infectious sequelae of food-borne disease.

Infectious gastroenteritis in the form of travelers' diarrhea (TD) is also a common cause of morbidity among travelers to developing regions of the world. One subpopulation of healthy travelers that has repeatedly shown a high burden of TD is deploying military personnel. Given the high rate of TD in this population as well as the association between TD and FGD, understanding the morbidity of these post-infectious sequelae is important.[8,9] The costs of these sequelae need to be considered for the relative assessment of travel and deployment health outcomes, as well as for an assessment of the value of current and future interventions. This assessment is important at both the individual and population levels. Health utility indices (HUIs),

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which value health states based on preferences for certain health outcomes, can be used as preference weights in the calculation of quality-adjusted life-years (QALYs) and are useful tools for assessing the impact of disease on health-related quality of life (HRQoL). A subset of these indices, known as generic preference instruments, involve surveys that define non-disease-specific health states that are valued by a sample population by various methods, such as Standard Gamble, Time Trade-Off, and the Visual Analogue Approach.[10] Examples include the HUI, European Quality of Life-5 Dimensions (EQ-5D), and the Short Form 36 (SF-36).

Given that data are lacking for common post-infectious FGD conditions, we sought to calculate HUI scores using data obtained from recently deployed military personnel completing an SF-36 as part of a prior research study,[11] and to compare these scores across FGD outcomes and component symptoms.

Methods

Data, described previously, were obtained from a web-based survey of US military personnel following deployment to Incirlik Air Base in Turkey or Multinational Force Observers (MFO) South Camp, Egypt.[11] The survey consisted of demographic information, diarrhea history during deployment, assessment of a number of chronic intestinal symptoms experienced during the past 3–6 months, and self-reported HRQoL using the SF-36. Participation was voluntary, and participants received a $15 gift certificate as compensation. TD was defined as having any episodes of diarrhea (three or more loose stools or liquid stools in a 24-hour period) during deployment, and FGD were characterized using the Rome II criteria.[12]

The SF-36 was transformed to a HUI, the SF-6D, as described by Brazier and colleagues.[13] Briefly, a subset of six dimensions of health (physical functioning, role limitations, social functioning, bodily pain, mental health, and vitality) is abstracted from the SF-36 to create the SF-6D health state classification. Each dimension contains between two and six levels, and a health state is defined for each of the six dimensions. Health states were valued by a sample population in the United Kingdom, and the valuations were modeled to calculate "coefficients" for each level of the six health dimensions. Additional modeling provided a method to estimate the remaining health states enabling calculation of HUIs for all SF-6D health states.[14]

Overall HUIs and reductions by each of the six dimensions were calculated for each subject and compared across five FGD: irritable bowel syndrome (IBS), dyspepsia, bloating, constipation, and diarrhea, clinical syndromes for which no structural, biochemical, or infectious etiology can be identified.[15] Additionally, HUIs were compared across specific symptoms to assess symptom impact on HRQoL. Statistical comparisons were made using a *t*-test or an analysis of variance (ANOVA) as appropriate. All statistical analyses were conducted using SAS version 9.3 (Cary, NC, USA) and interpreted using an $\alpha = 0.05$.

The study protocol was approved by the Institutional Review Board (IRB) of the US Naval Medical Research Unit No. 3, Cairo, Egypt, in compliance with all applicable federal regulations governing the protection of human subjects. The IRB waived the requirement for documentation of written informed consent for this web-based follow-up survey. This work was funded under the Armed Forces Health Surveillance Center—Global Emerging Infections Surveillance and Response System research program (Work Unit Number 847705.82000.25 GB.E0018). The study design, data collection, analysis, and interpretation as well as writing of the manuscript were the sole responsibility of the investigation team.

Results

The demographics of the study population have been reported previously and are generally reflective of deployed military personnel.[11] The most common FGD identified was bloating ($n = 28$, 23%), followed by IBS ($n = 17$, 14%), functional diarrhea ($n = 16$, 13%), functional constipation ($n = 12$, 10%), and dyspepsia ($n = 10$, 8%), though there was a significant overall overlap in functional diagnoses (Figure 1). Nearly half of the participants developed an FGD ($n = 58$, 48%), the majority (49/58, 84%) of which developed TD during deployment. The other nine FGD cases were unable to be linked to antecedent TD and were classified as "idiopathic."

The mean health dimension coefficient scores and SF-6D index score for each functional outcome are shown in Table 1 in comparison with those same parameters for those with no FGD. The largest, most consistent decrement in the overall SF-6D HUI across the FGD was associated with mental health (mean decrement ranging from −0.06 to 0.00) and vitality (mean decrement ranging from −0.06 to −0.07), while minimal decrements were observed for physical functioning and role participation. Those with no FGD had a significantly ($p < 0.001$) higher overall mean SF-6D index compared with those with any FGD (0.87 and 0.76, respectively). IBS and dyspepsia had the lowest index score, and every FGD, except for functional constipation and idiopathic FGD, had significantly reduced SF-6D utility scores compared with those with no FGD. There were no differences in health indices across gender, race, or military rank (data not shown).

A number of specific symptoms were associated with a significant reduction in SF-6D index scores (Table 2). The majority of these symptoms were temporally associated with bowel movements. Specifically, a noticed change in the frequency and consistency of bowel movements following abdominal and/or upper abdominal pain was an ~15% decrease in mean SF-6D utility scores (compared with those without those symptoms). Similarly, the presence of a myriad of symptoms in the

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Table 1 Mean (standard deviation) of health dimension coefficient scores and SF-6D index score

	Mean (SD) score								
						Any FGD			
	IBS	Dyspepsia	Functional bloating	Functional diarrhea	Functional constipation	All	Post-infectious	Idiopathic	No FGD
N	17	10	28	16	12	58	49	9	62
Physical functioning	−0.01(0.02)	−0.01(0.02)	−0.02(0.02)	−0.02(0.03)	−0.02(0.03)	−0.02(0.03)	−0.02(0.03)	0.00(0.01)	−0.01(0.02)
Role participation	−0.02(0.03)	−0.03(0.03)	−0.02(0.03)	−0.02(0.03)	0.0(0.02)	−0.02(0.03)	−0.02(0.03)	−0.01(0.02)	0.00(0.01)
Social functioning	−0.05(0.02)	−0.05(0.02)	−0.04(0.03)	−0.03(0.03)	−0.02(0.03)	−0.03(0.03)	−0.03(0.03)	−0.04(0.03)	−0.01(0.02)
Bodily pain	−0.05(0.02)	−0.04(0.02)	−0.04(0.03)	−0.02(0.02)	−0.02(0.03)	−0.03(0.03)	−0.03(0.03)	−0.02(0.02)	−0.02(0.02)
Mental health	−0.06(0.03)	−0.07(0.03)	−0.04(0.03)	−0.04(0.03)	0.00(0.04)	−0.05(0.03)	−0.04(0.03)	−0.06(0.04)	−0.02(0.03)
Vitality	−0.07(0.02)	−0.07(0.03)	−0.07(0.01)	−0.07(0.02)	−0.06(0.03)	−0.07(0.02)	−0.07(0.02)	−0.07(0.03)	−0.06(0.02)
SF-6D index	0.70(0.12)*	0.68(0.08)*	0.74(0.13)*	0.77(0.11)*	0.79(0.16)	0.76(0.12)*	0.75(0.12)*	0.78(0.13)	0.87(0.08)

IBS = irritable bowel syndrome; FGD = functional gastrointestinal disorders.
*Statistically significant ($p < 0.05$) difference in mean SF-6D index compared with no FGD.

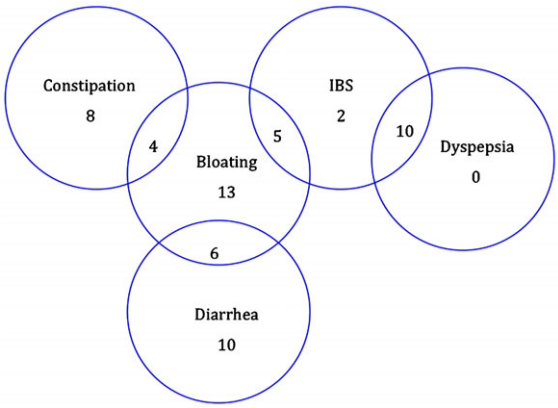

Figure 1 Venn diagram of the number of subjects with each functional gastrointestinal disorder.

3 months prior to survey completion was associated with a significant reduction in the HUI.

Discussion

Several studies have recently reported an increased risk of post-infectious functional bowel disorders following diarrhea during travel from developed to developing regions of the world.[11,16–21] These studies have increased the appreciation for TD as more than a simple nuisance illness limited to acute morbidity. While questions abound regarding infection etiology, host characteristics, and other stressors proximal to travel, studies repeatedly support a significant increase in the risk of FGD following acute infectious diarrhea. Importantly, little attention has been given to the impact of these chronic sequelae on travelers' health. Despite evidence that post-infectious and idiopathic FGD may have unique characteristics, estimates of disease morbidity are predominantly limited to FGD that may not be post-infectious.[22] This study extends our appreciation of FGD in a unique population of healthy travelers and should be repeated in other, more broadly, representative travel populations to enable refinement of morbidity estimates.

This study highlights the importance of FGD on overall health. Although we were unable to identify significant differences in the impact of post-infectious compared with idiopathic FGD, the high incidence of infectious diarrhea, especially among deployed military populations, highlights these sequelae as one of the important aspects in assessing the overall disease-related morbidity. A recent review estimating the burden of several post-deployment outcomes found that the disability ability adjusted life years (DALYs) due to TD sequelae are substantial and, when considered additively, approach those attributable to post-traumatic stress disorder (PTSD).[1] As that study emphasized, however, more investigation is needed to more accurately and comprehensively quantify the burden attributable to these sequelae, specifically with regard to the need for more disability weight estimates in studies among relevant populations.

A number of limitations on the use of the SF-6D arise from the method by which it was calculated. Limitations in the use of SF-6D include potential loss of information from the SF-36, reduced sensitivity at the upper levels of some health state dimensions, and systematic overprediction of poor health states.[13] Furthermore, there is potential bias in coefficients estimated for the levels of each health dimension, because in the original study, some health states were valued by the same respondent.[14] Additionally, valuations of the health states described by the SF-6D have thus far only been conducted in a sample population in the UK, which perhaps limits the applicability of the SF-6D index to other populations.

Importantly, this study was not a priori designed to assess differences in HUIs and as such, the results need to be interpreted with caution. Additionally, these data were obtained from a unique population and may not be reflective of the general travel population. Also of note is that we did not incorporate any measure of

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Table 2 Symptoms resulting in a significantly reduced SF-6D index score*

Symptom	Present		Absent		Mean difference (% change)	*p*-value
	N	Mean SF-6D	*N*	Mean SF-6D		
Continuous or nearly continuous abdominal pain over previous 6 months	10	0.71	105	0.82	−0.11(−13%)	0.024
After a bowel movement:						
upper abdomen discomfort or pain improvement	17	0.72	98	0.83	−0.11(−13%)	<0.001
abdominal discomfort or pain improvement	15	0.68	100	0.83	−0.15(−18%)	<0.001
When abdominal discomfort or pain starts:						
change in usual number of bowel movements	13	0.71	102	0.83	−0.12(−15%)	<0.001
stools are softer or harder than usual	15	0.70	100	0.83	−0.13(−16%)	<0.001
When upper abdominal discomfort or pain starts:						
change in usual number of bowel movements	14	0.73	101	0.83	−0.09(−12%)	0.005
stools are softer or harder than usual	16	0.73	99	0.83	−0.10(−12%)	0.002
Over past 3 months:						
frequent heartburn, burning pain, or discomfort in chest	29	0.76	86	0.83	−0.08(−8%)	0.002
frequent discomfort or pain in upper abdomen	20	0.75	95	0.83	−0.07(−10%)	0.009
frequent discomfort or pain in abdomen	17	0.71	98	0.83	−0.13(−15%)	<0.001
loose, mushy, watery stool > 75% of bowel movements	27	0.75	88	0.83	−0.08(−10%)	0.001
frequent pain that awakens and/or interferes with sleep	12	0.74	103	0.82	−0.08(−10%)	0.003
any visible blood in stools	8	0.73	107	0.82	−0.09(−11%)	0.039
an unexplained fever	8	0.67	107	0.83	−0.16(−19%)	<0.001
Over past 3 months, >25% of the time:						
more than three bowel movements a day	23	0.76	92	0.83	−0.06(−8%)	0.021
loose, mushy, or watery stools	52	0.77	63	0.85	−0.08(−9%)	<0.001
straining during a bowel movement	35	0.76	80	0.84	−0.08(−10%)	0.001
having to rush to toilet to have a bowel movement	37	0.75	78	0.84	−0.09(−11%)	<0.001
passing mucus (slime) during a bowel movement	17	0.74	98	0.83	−0.08(−11%)	0.006
abdominal fullness, bloating, or swelling	33	0.73	82	0.85	−0.12(−14%)	<0.001
sensation that stool is blocked when having a bowel movement	20	0.77	95	0.82	−0.06(−6%)	0.039
a need to press on or around the anus or vagina to try to remove stool to complete the bowel movement	12	0.72	103	0.82	−0.10(−12%)	0.004

*"Frequent" is defined as the symptom being present during at least 3 weeks (at least once a week) in the last 3 months.

disease persistence and/or stability nor how health utility measures may have changed over time. Porter and colleagues recently estimated just short of 700 years lived with disability (YLD) associated with IBS per 100,000 person-years of deployment presuming a 1-year illness duration.[1] This was directly comparable to ~1,200 for PTSD over that same duration indicating that these chronic sequelae may reflect significant morbidity to an otherwise healthy adult population.

Despite statistical significance, one is left to consider the "clinical significance" of the observed differences in the SF-6D scores between those with and without FGD.[23] Although the clinical meaning of the SF-6D differences reported here is likely best determined in longitudinal studies on worsening or improving FGD, some inferences can be made based on other disease states albeit in different populations. Among 305 Australians with spinal cord injuries, SF-6D changes of −0.12 were observed in subjects who developed a urinary tract infection (UTI) compared with baseline and compared with those without a UTI.[24] Those estimates are comparable to differences observed here. Others have attempted to define a minimally important difference (MID) in SF-6D scores to determine the smallest change that is clinically meaningful with values ranging from 0.01 to 0.10.[25,26] More specific to FGD, Akehurst and colleagues described changes in quality of life measures from IBS cases in the UK with a mean MID of 0.022 (standard deviation: 0.096).[26,27] Although SF-6D scores reported here (0.87 and 0.76) appear to represent clinically meaningful differences, additional longitudinal studies in this population are needed to better understand these values.

Future studies should assess the use of other HRQoL indices and methods for comparison, for better understanding of the responsiveness of the SF-6D and to confirm the results observed here. To circumvent some of the limitations herein, such studies should be conducted with a much larger sample size and include prospective, long-term follow-up data. Furthermore, to gain better understanding of the long-term health impact of these post-TD FGD, it would also be important to assess HRQoL over a period of time following disease onset to assess for variability in quality of life measures and to establish the duration of impact.

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Declaration of Interests

The authors declare that they have no competing interests.

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