Table 1 (*continued*)

	Men					Women				
	Low strain	Active job	Passive job	Strain job	p^a	Low strain	Active job	Passive job	Strain job	p^a
Current smoker (< = 20/day)	36.8	33.9	38.9	34.7		6.2	6.5	6.1	5.2	
Current smoker (>20/day)	19.0	20.1	15.0	18.4		0.2	0.2	0.3	0.2	
Alcohol intake (g/day)										
Non-drinker	20.0	20.4	25.5	18.4	0.003	71.1	65.3	74.0	68.3	0.002
<28.9	32.3	30.1	28.4	27.3		23.0	28.6	21.2	27.2	
⩾28.9	47.7	49.5	46.1	54.3		5.9	6.1	4.8	4.5	
Physical activity index[b]										
⩽28	18.7	17.0	18.9	20.2	<0.001	24.3	22.4	28.3	27.6	<0.001
29–36	38.8	34.7	44.2	32.4		49.2	46.7	54.3	50.9	
⩾37	42.5	48.3	36.9	47.4		26.4	30.9	17.4	21.5	
Biological characteristics										
Body mass index (kg/m^2) (%)										
<22	35.5	32.9	39.8	39.7	0.007	33.5	38.0	40.3	41.9	0.049
22–24.9	40.2	40.9	40.3	36.9		40.2	38.6	37.6	35.8	
⩾25	24.3	26.2	19.9	23.4		26.3	23.4	22.2	22.2	
Mean total cholesterol (mg/dl)	188.7	186.8	182.2	186.3	0.002	192.5	192.3	192.3	191.2	0.877
Hypertension[c] (%)	19.6	23.8	26.2	26.3	0.024	20.4	18.0	18.0	17.1	0.423
Diabetes mellitus[d] (%)	5.3	5.6	6.7	5.3	0.577	1.3	1.7	2.6	2.6	0.186

[a]Tests for heterogeneity.

[b]Physical activity index refers to metabolic equivalent task (MET) hours.

[c]Individuals were classified as hypertensive if (1) their systolic blood pressure was equal to or greater than 160 mmHg, (2) their diastolic blood pressure was equal to or greater than 90 mmHg, or (3) they were clinically diagnosed as hypertensive.

[d]Presence of diabetes was defined as (1) a fasting blood glucose level of at least 126 mg/dl, (2) a casual blood glucose level of at least 200 mg/dl, or (3) in treatment.

coefficient alphas for the job control index and psychological demand index were 0.65 and 0.69, respectively. The job conditions assessed as part of this cohort during the follow-up demonstrated a moderate degree of stability, with 5-year-interval intraclass correlation coefficients of 0.63 ($n = 377$) for job control and 0.55 ($n = 378$) for job demands (Kayaba et al., 2005).

The scores for each index were categorized using the median, and the two categorical variables were used to determine the four-level rank-ordered job-strain variables corresponding to Karasek's 2×2 model of job demand–control, with low job demand and high job control representing a low-strain job (reference category), high job demand and high job control representing an active job, low job demand and low job control representing a passive job, and high job demand and low job control representing a strain job.

Statistical analysis

The relationships between psychosocial job characteristics and the studied variables at baseline were examined using the χ^2 test for discrete variables and analysis of variance for continuous variables. Person-years of follow-up were counted for each participant from the date of her/his health examination to the date of death, date of emigration outside the study community, or the end of 2002, whichever occurred first. Data on emigration of the study population were obtained every year from the participants' municipal governments. A total of 159 subjects (2.4% of the analytic cohort) moved out of their communities during the follow-up and were analyzed as censored cases. The mean length of the follow-up was 9.4 years. The total observed person-years was 60,831. Cox's proportional hazard regression analysis was used to examine the association between psychosocial job characteristics and mortality after adjusting for age (18–39, 40–49, 50–59, and 60–65 years, respectively), educational attainment ($\leqslant$15 years: age at completion of compulsory education, 16–18 years: age at finishing senior high school, $\geqslant$19 years: age at entering college or further education), occupation (five strata: managers, professionals/technicians/clerks, sales/service workers, farming/forestry/fishery, security/transportation/communications/craft workers/labourers/unclassified), smoking status (lifetime non-smoker, ex-smoker, current light smoker ($\leqslant$20/day), current heavy smoker ($>$20/day)), alcohol consumption (non-drinker, <1 *go* daily (*go*, a traditional Japanese alcohol unit; 1 *go* = 28.9 g of alcohol), $\geqslant 1$ *go* daily), physical activity index (Kannel & Sorlie, 1979) ($<$29, 29–36, $\geqslant$37), body mass index ($<$22, 22–24.9, $\geqslant$25 kg/m^2), hypertension, diabetes, total cholesterol and study community. Covariate variables were measured at baseline. Ordinal or nominal variables were represented by dummy variables, and serum total cholesterol was analyzed as a continuous variable. In sub-analyses, we utilized categories based on individual quartiles of the demand and control scores as the main exposure to see which component contributes more to the effect. Statistical tests were two-tailed. All analyses were conducted with SPSS for Windows, release 13.

The study design and procedures were reviewed and approved by each municipal government and the Ethics Committee for Epidemiological Research at Jichi Medical School. Written informed consent was obtained from all prospective participants.

Results

Table 1 shows the relationships between psychosocial job characteristics and the studied variables at baseline. Men reporting active jobs were younger, and those with passive jobs older. The socioeconomic status was lower in men with passive or strain jobs than in those with active or low-strain jobs; the former group was more likely to be engaged in blue-collar work and have less education. Prevalence of pre-industrial occupations (farming/forestry/fishery) was high among men with low strain jobs, while managers were prevalent among men with active jobs. Men exposed to job strain were more likely to be heavy drinkers. Men with active jobs had a higher level of physical activity. Body mass index and total cholesterol levels were lowest in men with passive jobs, while the prevalence of hypertension was highest in men exposed to job strain.

Women with low-strain jobs were older and more obese. The relationship between psychosocial job characteristics and socioeconomic status was similar to that of men. Active jobs were associated with alcohol consumption and a high level of physical activity.

During the follow-up, 157 men and 64 women died (Table 2). Men with active jobs had the lowest mortality rates among the job demand–control categories. The adjusted relative risk of mortality

Table 2
Adjusted relative risk of all-cause mortality by levels of psychosocial job characteristics, male and female workers aged 65 and under and free from cancer and cardiovascular diseases, the Jichi Medical School Cohort Study, 1992/1995–2002

Job characteristics category	No. of cases	Person-years of follow-up	Age-adjusted		Multivariate	
			RR[a]	95% CI[a]	RR[b]	95% CI
Men						
Low strain[c]	32	4572	1.00		1.00	
Active job	28	8936	0.50	0.30, 0.83	0.53	0.31, 0.89
Passive job	55	8476	0.83	0.54, 1.28	0.87	0.55, 1.40
Strain job	42	7630	0.79	0.50, 1.26	0.79	0.47, 1.31
Women						
Low strain[c]	18	6234	1.00		1.00	
Active job	15	8818	0.68	0.34, 1.35	0.76	0.35, 1.65
Passive job	16	8523	0.67	0.34, 1.32	0.78	0.37, 1.65
Strain job	15	7640	0.76	0.38, 1.51	0.72	0.32, 1.64

[a]RR, relative risk; CI, confidence interval.
[b]Adjusted for age (18–39, 40–49, 50–59, or 60–65), educational attainment (age at completion; ⩽15, 16–18, ⩾19), occupation (managers, professionals/technicians/clerks, sales/service workers, farming/forestry/fishery, or security/transportation/communications/craft workers/labourers/unclassified), smoking (lifetime non-smoker, ex-smoker, current light smoker (⩽20/day), or current heavy smoker (>20/day)), alcohol intake (non-drinker, <28.9 g/day, or ⩾28.9 g/day), physical activity index (⩽28, 29–36, or ⩾37), body mass index (kg/m^2; <22, 22–24.9, or ⩾25), total cholesterol (mg/dl), hypertension (yes/no), diabetes (yes/no), and the community.
[c]Reference category.

was reduced by almost one-half among individuals with active jobs and this reduction was statistically significant. In women, no statistically significant differences were found for mortality among the job characteristic categories.

A separate investigation of the effects of job control and demands showed that men with lower job control tended to have a higher risk of mortality, but the associations were not significant. The relative risk for the second-highest job demands was significantly below 1.0, and the test for trends showed a tendency towards a protective effect. Among women, point estimates of the effects of job control and demands on mortality were in unexpected directions, but were statistically insignificant (Table 3).

Analyses of cause-specific mortality might explain some mechanisms of the association between psychosocial job characteristics and mortality. The associations with mortality from cancer (ICD 10th revision codes C00 to D48), cardiovascular diseases (ICD 10th revision codes I00–I52 and I60–I69) and external causes (ICD 10th revision codes V01–Y98) were examined separately. Because the number of deaths was particularly small among women, we pooled the data for men and women. The interaction between psychosocial job characteristics and sex was not statistically significant, so further analyses were based on the total sample and sex was adjusted for in each Cox's proportional hazard regression model (Table 4).

A total of 102 workers (66 men and 36 women) died of cancer. The site-trend of cancer deaths in our study population was similar to the national data (Statistics and Information Department, 2002; Appendix A). The multivariate relative risk of cancer mortality was lowest among workers with active jobs. We re-ran the analysis for smoking-related cancers (lip, oral cavity and pharynx ($n = 2$), oesophagus (1), stomach (14), liver (8), pancreas (7), bronchus and lung (23), kidney (1), myeloid leukaemia (2)), producing similar results to the analysis of total cancers, though the findings were statistically insignificant. Compared with the low-strain category, the multivariate relative risk of an active job was 0.46 (95% CI: 0.19, 1.07; $p = 0.070$).

A total of 35 workers (25 men and 10 women) died of cardiovascular diseases. The patterns for cardiovascular disease mortality were somewhat different from those of all-cause mortality. Workers exposed to job strain had the highest risk of cardiovascular mortality, and those with low strain had the lowest. But there were no statistically significant differences.

A total of 45 workers (37 men and 8 women) died of external causes. The relative risk for external causes of mortality was lowest among workers with job strain, but associations were not statistically significant.

Table 3
Multivariate relative risk of all-cause mortality by levels of job control and job demands, male and female workers aged 65 and under and free from cancer and cardiovascular diseases, the Jichi Medical School Cohort Study, 1992/1995–2002

Levels of job control and job demands	No. of cases	Person-years of follow-up	Multivariate[a]	
			RR[b]	95% CI[b]
Men				
Level of control				
Highest[c]	18	4599	1.00	
Higher middle	42	8909	0.99	0.56, 1.75
Lower middle	53	8437	1.25	0.70, 2.20
Lowest	44	7670	1.11	0.61, 2.01
p for trend[d]				0.527
Level of demand				
Lowest[c]	65	8731	1.00	
Lower middle	22	4318	0.87	0.52, 1.45
Higher middle	36	8579	0.60	0.39, 0.94
Highest	34	7987	0.76	0.48, 1.19
p for trend[d]				0.078
Women				
Level of control				
Highest[c]	14	6390	1.00	
Higher middle	19	8663	0.97	0.44, 2.13
Lower middle	20	9654	0.87	0.39, 1.91
Lowest	11	6509	0.82	0.33, 2.04
p for trend[d]				0.618
Level of demand				
Lowest[c]	16	5914	1.00	
Lower middle	18	8843	0.83	0.40, 1.72
Higher middle	16	8810	0.76	0.36, 1.61
Highest	14	7649	0.79	0.35, 1.74
p for trend[d]				0.523

[a]Adjusted for age (18–39, 40–49, 50–59, or 60–65), educational attainment (age at completion; ⩽15, 16–18, ⩾19), occupation (managers, professionals/technicians/clerks, sales/service workers, farming/forestry/fishery, or security/transportation/communications/craft workers/labourers/unclassified), smoking (lifetime non-smoker, ex-smoker, current light smoker (⩽20/day), or current heavy smoker (>20/day)), alcohol intake (non-drinker, <28.9 g/day, or ⩾28.9 g/day), physical activity index (⩽28, 29–36, or ⩾37), body mass index (kg/m^2; <22, 22–24.9, or ⩾25), total cholesterol (mg/dl), hypertension (yes/no), diabetes (yes/no), and the community.
[b]RR, relative risk; CI, confidence interval.
[c]Reference category.
[d]Tests for trends were performed by modelling the group scores of psychosocial work variables (1, 2, 3) as one variable.

Discussion

Among a community-based Japanese working population, the job strain hypothesis was not supported with regard to all-cause mortality. However, men with active jobs had the lowest mortality risk from all causes; both high job control and high job demands had a small, statistically insignificant protective effect against mortality. Cause-specific analyses revealed that this finding was most likely explained by the association between active jobs and low cancer mortality. To the best of our knowledge, this is the first prospective report, other than those in western societies, to address psychosocial job characteristics and mortality. The job demand–control model was developed in western populations, and although growing research suggests its applicability to Japanese populations (Kawakami et al., 2000; Kawakami, Haratani, & Araki, 1998; Tsutsumi, Kayaba, Ishikawa et al., 2003; Tsutsumi et al., 2001; Tsutsumi, Kayaba, Yoshimura et al., 2003; Yoshimasu & The Fukuoka Heart Study Group, 2001), prospective studies have been warranted as evidence has been limited to cross-sectional or case–control studies.

Men with active jobs had the lowest all-cause mortality, and this finding appeared largely attributable to a reduction in cancer mortality. A

Table 4
Adjusted relative risk of cause-specific mortality by levels of psychosocial job characteristics, male and female workers aged 65 and under and free from cancer and cardiovascular diseases, the Jichi Medical School Cohort Study, 1992/1995–2002

Job characteristics category	No. of cases	Age, sex-adjusted		Multivariate	
		RR[a]	95% CI[a]	RR[b]	95% CI
Cancer mortality					
Low strain[c]	27	1.00		1.00	
Active job	22	0.53	0.30, 0.93	0.55	0.30, 1.00
Passive job	29	0.61	0.38, 1.04	0.64	0.36, 1.12
Strain job	26	0.67	0.39, 1.16	0.72	0.40, 1.30
Cardiovascular diseases mortality					
Low strain[c]	4	1.00		1.00	
Active job	7	1.18	0.34, 4.05	1.15	0.33, 4.01
Passive job	12	1.63	0.52, 5.06	1.74	0.54, 5.64
Strain job	12	2.47	0.81, 7.51	1.98	0.59, 6.70
External causes of mortality					
Low strain[c]	10	1.00		1.00	
Active job	11	0.62	0.26, 1.46	0.71	0.28, 1.79
Passive job	17	0.95	0.43, 2.08	0.95	0.39, 2.31
Strain job	7	0.45	0.17, 1.17	0.44	0.15, 1.30

[a]RR, relative risk; CI, confidence interval.
[b]Adjusted for sex, age (18–39, 40–49, 50–59, or 60–65), educational attainment (age at completion; $\leqslant$15, 16–18, $\geqslant$19), occupation (managers, professionals/technicians/clerks, sales/service workers, farming/forestry/fishery, or security/transportation/communications/craft workers/labourers/unclassified), smoking (lifetime non-smoker, ex-smoker, current light smoker ($\leqslant$20/day), or current heavy smoker ($>$20/day)), alcohol intake (non-drinker, $<$28.9 g/day, or $\geqslant$28.9 g/day), physical activity index ($\leqslant$28, 29–36, or $\geqslant$37), body mass index (kg/m^2; $<$22, 22–24.9, or $\geqslant$25), total cholesterol (mg/dl), hypertension (yes/no), diabetes (yes/no), and the community.
[c]Reference category.

definite conclusion as to the association between active jobs and cancer awaits further investigations, because despite the heavy health burden of cancer evidence regarding the connection between job characteristics and cancer is scarce and inconsistent (Achat, Kawachi, Byrne, Hankinson, & Colditz, 2000; Courtney, Longnecker, & Peters, 1996; Jansson et al., 2004; Schernhammer et al., 2004; Spiegelman & Wegman, 1985). Moreover, as of yet there is no direct biological evidence regarding an association. However, since suppression of immune function is suspected among middle-aged men exposed to adverse job characteristics, in particular low job control (Kawakami et al., 1997; Nakata et al., 2002), more insight might be gained by investigating the effects of psychosocial job characteristics on cancer.

Point estimates of the effect of job strain on cardiovascular disease mortality were consistent with the strain hypothesis, but observed associations were small in magnitude and did not reach a level of statistical significance. The age-adjusted mortality rates for ischaemic heart diseases among Japanese represent the internationally lowest levels (National Heart Lung and Blood Institute, 1993). If job strain exerts its effects primarily through ischaemic heart diseases, the impact of job strain on cardiovascular mortality in Japan should be weaker than in western countries where mortality due to ischaemic heart diseases is much higher. The inconclusive findings to date therefore warrant further examination of the effect of job strain on cardiovascular outcome.

The results showed no statistically significant associations in women, consistent with previous studies (Achat et al., 2000; Belkić, Landsbergis, Schnall, & Baker, 2004; Hall, Johnson, & Tsou, 1993; Lee et al., 2002). In addition to the limited number of outcome cases and incomplete adjustment for gender-related confounding variables such as home-work interference, we should also bear in mind that the labour force participation rate of Japanese women is lower than that in western societies. Except for large enterprises, female attitudes toward work might therefore be less proactive. Inclusion of part-time workers, the majority of whom are assumed to be women, might also have affected the results.

Autonomy for decision making was measured using two parameters: the right to make one's own decisions and freedom to choose the manner in which the work is performed. Since our database included a large proportion of managers and employers (presumably including a large number of self-employed), we tested the importance of the above measures in these two groups. The level of decision authority was significantly higher among managers and employers than respective counterpart groups. Moreover, in these sub-groups, those with the highest decision authority had the lowest mortality risk but the association was not statistically significant (data not shown).

Limitations

The study population was composed of relatively healthy Japanese adults, mortality rates for whom are considerably below those of the general population (Ishikawa et al., 2002). The mass screening examination programme is not mandatory and employees who undergo health-checks at their workplaces do not have to participate. Thus, participants might have a more health-oriented predisposition than non-participants. In addition, the invitation to participate did not insist that those receiving care for cardiovascular diseases should sign up. Moreover, participants were relatively old, and thus, a considerable number might have sustained a long career with the same job (the healthy worker effect). Furthermore, the follow-up was short. All these conditions probably accounted for the small number of outcome events. In addition, the relatively low response rate might imply that workers with demanding work situations did not participate in the programme. Consequently, the results probably give a conservative estimate of the risk of job strain on mortality. Workers with major diseases at baseline were excluded from the analyses, but some individuals might have changed their jobs according to their *pre*-clinical health condition (Karasek, Schwartz, & Theorell, 1982). If participants shifted to less-demanding jobs because of health problems, there would be selection bias leading to underestimation of the association between job strain and mortality on one hand and an overestimation of the association between active jobs and 'low' mortality on the other. Lastly, since under-representation of those with access to occupational health limits generalizability of the findings, replication is needed in the future among representative samples of employed workers.

There is great potential for confounding of the association between job characteristics and cancer mortality; those in active jobs were younger, of higher socioeconomic status and physically active. We took into account relevant covariate variables in the analyses, but there is still room for residual confounding. For example, negative emotions such as hostility and depression (Williams et al., 1997) as well as employment status (full- vs. part-time) and income level were not measured. Immunologic factors are another plausible pathway.

All-cause mortality is too vague an outcome to explore the exact mechanisms through which psychosocial job characteristics affect the health of workers. Many diseases contribute to mortality with a different incidence according to the population examined. The same is true for cancers as a single group, since cancer is a heterogeneous mix of specific cancers with different causes. Research on one specific type of cancer is therefore important in accurately examining the role of stress in the development of cancer (Burke & Goodkin, 1997). In addition, non-fatal cases were not considered in this study, and thus, the incidence of defined diseases among Japanese workers should be addressed in the future.

Cronbach's alpha coefficient of job control was slightly low, and our exposure assessment was limited to one point in time; both likely caused associations toward the null. However, statistically significant long-term stability was confirmed in our measurements (Kayaba et al., 2005). Moreover, previous studies have shown the importance of cumulative job control (Bosma et al., 1997) and an active job as a protector (Amick et al., 2002; Johnson, Stewart, Hall, Fredlund, & Theorell, 1996).

Despite the above, our study had a number of strengths. For example, the study population is the largest Japanese cohort of this kind to date. Moreover, information about exposure to job strain was obtained from self-reports with a validated instrument rather than by assigning scores based on job description; hence, each score accurately represents individual work environments (Belkić et al., 2004). Self-reporting bias is unlikely to be important because of the hard endpoint (mortality) and prospective study design, and bias attributable to sample attrition is thought to be implausible as the follow-up rate was high.

Our study adds to the literature on demand–control psychosocial job characteristics and workers' health in a non-western society. In this Japanese working population, job strain did not predict all-cause mortality. However, further evaluation of the hypothesis that active jobs have beneficial effects on, for example, active learning behaviour and/or personal growth, both of which could potentially improve health (Theorell & Karasek, 1996), is warranted. Moreover, investigation of the effect of psychosocial job characteristics on cancer might provide valuable insights into the health of workers.

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Appendix A. Cancer mortality by site, male and female workers aged 65 and under and free from cancer and cardiovascular diseases, the Jichi Medical School Cohort Study, 1992/1995–2002

Sites	*n*
Lip, oral cavity and pharynx	2
Digestive organs	
Stomach	14
Colon	7
Other sites	18
Respiratory and intrathoracic organs	
Bronchus and lung	23
Other sites	1
Breast	1
Female genital organs	7
Male genital organs	1
Urinary tract	1
Eye, brain and other parts of central nervous system	3
Thyroid and other endocrine glands	1
Malignant neoplasms of ill-defined, secondary and unspecified sites	16
Lymphoid/haematopoietic	6
Neoplasms of uncertain or unknown behaviour	1
Total	102

Appendix B

The Jichi Medical School Cohort Study Group: Akizumi Tsutsumi (University of Occupational and Environmental Health), Atsushi Hashimoto (Aichi Prefectural Aichi Hospital), Eiji Kajii (Jichi Medical School), Hideki Miyamoto (former Jichi Medical School), Hidetaka Akiyoshi (Fukuoka University School of Medicine), Hiroshi Yanagawa (Saitama Prefectural University), Hitoshi Matsuo (Gifu Prefectural Hospital), Jun Hiraoka (Tako Central Hospital), Kaname Tsutsumi (Kyushu International University), Kazunori Kayaba (Saitama Prefectual University), Kazuomi Kario, Kazuyuki Shimada (Jichi Medical School), Kenichiro Sakai (Akaike Town Hospital), Kishio Turuda (Takasu National Health Insurance Clinic), Machi Sawada (Agawa Osaki National Health Insurance Clinic), Makoto Furuse (Jichi Medical School), Manabu Yoshimura (Kuze Clinic), Masahiko Hosoe (Gero Hot-Spring Hospital), Masahiro Igarashi (Igarashi Clinic), Masafumi Mizooka (Kamagari National Health Insurance Clinic), Naoki Nago (Yokosuka General Hospital Uwamachi), Nobuya Kodama (Sakugi Clinic), Noriko Hayashida (Tako Central Hospital), Rika Yamaoka (Awaji-Hokudan Public Clinic), Seishi Yamada (Wara National Health Insurance Hospital), Shinichi Muramatsu, Shinya Hayasaka, Shizukiyo Ishikawa (Jichi Medical School), Shuzo Takuma (Akaike Town Hospital), Tadao Gotoh (Wara National Health Insurance Hospital), Takafumi Natsume (Oyama Municipal Hospital), Takashi Yamada (Kuze Clinic), Takeshi Miyamoto (former Okawa Komatsu National Health Insurance Clinic), Tomohiro Deguchi (Akaike Town Hospital), Tomohiro Saegusa (Sakuma National Health Insurance Hospital), Yoshihiro Shibano (Saiseikai Iwaizumi Hospital) Yoshihisa Ito (Asahikawa Medical College), and Yosikazu Nakamura (Jichi Medical School).

References

Achat, H., Kawachi, I., Byrne, C., Hankinson, S., & Colditz, G. (2000). A prospective study of job strain and risk of breast cancer. *International Journal of Epidemiology, 29*, 622–628.

Alfredsson, L., Spetz, C.-L., & Theorell, T. (1985). Type of occupation and near-future hospitalization for myocardial infarction and some other diagnoses. *International Journal of Epidemiology, 14*(3), 378–388.

Alterman, T., Shekelle, R. B., Vernon, S. W., & Burau, K. D. (1994). Decision latitude, psychologic demand, job strain, and

coronary heart disease in the Western Electric Study. *American Journal of Epidemiology, 139*(6), 620–627.

Amick, B. C., 3rd., McDonough, P., Chang, H., Rogers, W., Pieper, C., & Duncan, G. (2002). Relationship between all-cause mortality and cumulative working life course psychosocial and physical exposures in the United States labor market from 1968 to 1992. *Psychosomatic Medicine, 64*(3), 370–381.

Åstrand, N.-E., Hanson, B. S., & Isacsson, S.-O. (1989). Job demands, job decision latitude, job support, and social network factors as predictors of mortality in a Swedish pulp and paper company. *British Journal of Industrial Medicine, 46*, 334–340.

Belkić, K., Landsbergis, P. A., Schnall, P. L., & Baker, D. (2004). Is job strain a major source of cardiovascular disease risk? *Scandinavian Journal of Work & Environmental Health, 30*(4), 85–128.

Bosma, H., Marmot, M. G., Hemingway, H., Nicholson, A. C., Brunner, E., & Stansfeld, S. A. (1997). Low job control and risk of coronary heart disease in Whitehall II (prospective cohort) study. *British Medical Journal, 314*, 558–565.

Bosma, H., Peter, R., Siegrist, J., & Marmot, M. (1998). Two alternative job stress models and the risk of coronary heart disease. *American Journal of Public Health, 88*(1), 68–74.

Burke, M. A., & Goodkin, K. (1997). Stress and the development of breast cancer: A persistent and popular link despite contrary evidence. *Cancer, 79*(5), 1055–1059.

Courtney, J. G., Longnecker, M. P., & Peters, R. K. (1996). Psychosocial aspects of work and the risk of colon cancer. *Epidemiology, 7*(2), 175–181.

de Bacquer, D., Pelfrene, E., Clays, E., Mak, R., Moreau, M., de Smet, P., et al. (2005). Perceived job stress and incidence of coronary events: 3-year follow-up of the Belgian job stress project cohort. *American Journal of Epidemiology, 161*(5), 434–441.

Eaker, E., Sullivan, L., Kelly Hayes, M., D'Agostino, R. S., & Benjamin, E. (2004). Does job strain increase the risk for coronary heart disease or death in men and women? The Framingham offspring study. *American Journal of Epidemiology, 159*(10), 950–958.

Falk, A., Hanson, B. S., Isacsson, S.-O., & Östergren, P.-O. (1992). Job strain and mortality in elderly men: Social network, support, and influence as buffers. *American Journal of Public Health, 82*(8), 1136–1139.

Haan, M. N. (1988). Job strain and ischaemic heart disease: An epidemiologic study of metal workers. *Annals of Clinical Research, 20*, 143–145.

Hall, E. M., Johnson, J. V., & Tsou, T. S. (1993). Women, occupation, and risk of cardiovascular morbidity and mortality. *Occupational Medicine—State of the Art Reviews, 8*(4), 709–719.

Ishikawa, S., Gotoh, T., Nago, N., Kayaba, K. & Jichi Medical School (JMS) Cohort Study Group. (2002). The Jichi Medical School (JMS) cohort study: Design, baseline data and standardized mortality ratios. *Journal of Epidemiology, 12*(6), 408–417.

Jansson, C., Johansson, A. L., Jeding, K., Dickman, P. W., Nyren, O., & Lagergren, J. (2004). Psychosocial working conditions and the risk of oesophageal and gastric cardiac cancers. *European Journal of Epidemiology, 19*(7), 631–641.

Johnson, J. V., Stewart, W., Hall, E. M., Fredlund, P., & Theorell, T. (1996). Long-term psychosocial work environment and cardiovascular mortality among Swedish men. *American Journal of Public Health, 86*(3), 324–331.

Kannel, W. B., & Sorlie, P. (1979). Some health benefits of physical activity: The Framingham study. *Archives of Internal Medicine, 139*(2), 857–861.

Karasek, R., Baker, D., Marxer, F., Ahlbom, A., & Theorell, T. (1981). Job decision latitude, job demands, and cardiovascular disease: A prospective study of Swedish men. *American Journal of Public Health, 71*(7), 694–705.

Karasek, R., & Theorell, T. (1990). *Healthy work: Stress, productivity, and the reconstruction of working life*. New York: Basic Books.

Karasek, R. A., Schwartz, J. E., & Theorell, T. (1982). *Stress at work and cardiovascular disease*. New York: Columbia University.

Kawakami, N., Akachi, K., Shimizu, H., Haratani, T., Kobayashi, F., Ishizaki, M., et al. (2000). Job strain, social support in the workplace, and haemoglobin A1c in Japanese men. *Occupational and Environmental Medicine, 57*, 805–809.

Kawakami, N., Haratani, T., & Araki, S. (1998). Job strain and arterial blood pressure, serum cholesterol, and smoking as risk factors for coronary heart disease in Japan. *International Archives of Occupational and Environmental Health, 71*, 429–432.

Kawakami, N., Tanigawa, T., Araki, S., Nakata, A., Sakurai, S., Yokoyama, K., et al. (1997). Effects of job strain on helper-inducer (CD4+CD29+) and suppressor-inducer (CD4+CD45RA+) T cells in Japanese blue-collar workers. *Psychotherapy and Psychosomatics, 66*, 192–198.

Kayaba, K., Tsutsumi, A., Gotoh, T., Ishikawa, S., & Miura, Y. (2005). Five-year stability of job characteristics scale scores among a Japanese working population. *Journal of Epidemiology, 15*(6), 228–234.

Kivimäki, M., Leino-Arjas, P., Luukkonen, R., Riihimaki, H., Vahtera, J., & Kirjonen, J. (2002). Work stress and risk of cardiovascular mortality: Prospective cohort study of industrial employees. *British Medical Journal, 325*(7369), 857–860.

Kuper, H., & Marmot, M. (2003). Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. *Journal of Epidemiology and Community Health, 57*(2), 147–153.

Lee, S., Colditz, G., Berkman, L., & Kawachi, I. (2002). A prospective study of job strain and coronary heart disease in US women. *International Journal of Epidemiology, 31*, 1147–1153.

Nakata, A., Tanigawa, T., Fujioka, Y., Kitamura, F., Iso, H., & Shimamoto, T. (2002). Association of low job control with a decrease in memory (CD4+CD45RO+) T lymphocytes in Japanese middle-aged male workers in an electric power plant. *Industrial Health, 40*(2), 142–148.

National Heart Lung and Blood Institute. (1993). *International activities report, fiscal year 1993*. Bethesda, USA: National Heart, Lung and Blood Institute.

Reed, D. M., LaCroix, A. Z., Karasek, R. A., Miller, D., & MacLean, C. A. (1989). Occupational strain and the incidence of coronary heart disease. *American Journal of Epidemiology, 129*(3), 495–502.

Schernhammer, E. S., Hankinson, S. E., Rosner, B., Kroenke, C. H., Willett, W. C., Colditz, G. A., et al. (2004). Job stress and breast cancer risk: The Nurses' Health Study. *American Journal of Epidemiology, 160*(11), 1079–1086.

Spiegelman, D., & Wegman, D. H. (1985). Occupation-related risks for colorectal cancer. *Journal of the National Cancer Institute*, *75*(5), 813–821.

Statistics and Information Department, Minister's Secretariat, Ministry of Health Labour and Welfare. (2002). *Vital statistics of Japan*. Tokyo: Health and Welfare Statistics Association.

Steenland, K., Johnson, J., & Nowlin, S. (1997). A follow-up study of job strain and heart disease among males in the NHANES1 population. *American Journal of Industrial Medicine*, *31*, 256–260.

Suadicani, P., Hein, H. O., & Gyntelberg, F. (1993). Are social inequalities as associated with the risk of ischaemic heart disease a result of psychosocial working conditions? *Atherosclerosis*, *101*, 165–175.

Theorell, T., & Karasek, R. A. (1996). Current issues relating to psychosocial job strain and cardiovascular disease research. *Journal of Occupational Health Psychology*, *1*(1), 9–26.

Tsutsumi, A., Kayaba, K., Ishikawa, S., Gotoh, T., Nago, N., Yamada, S., et al. (2003). Job characteristics and serum lipid profile in Japanese rural workers: The Jichi Medical School Cohort Study. *Journal of Epidemiology*, *13*(2), 63–71.

Tsutsumi, A., Kayaba, K., Tsutsumi, K., & Igarashi, M. (2001). Association between job strain and prevalence of hypertension: A cross sectional analysis in a Japanese working population with a wide range of occupations: The Jichi Medical School Cohort Study. *Occupational and Environmental Medicine*, *58*(6), 367–373.

Tsutsumi, A., Kayaba, K., Yoshimura, M., Sawada, M., Ishikawa, S., Sakai, S., et al. (2003). Association between job characteristics and health behaviors in Japanese rural workers. *International Journal of Behavioral Medicine*, *10*(2), 125–142.

Uehata, T. (1993). Stress, life style and health. *Bulletin of the Institute of Public Health*, *42*(3), 385–401.

Williams, R., Barefoot, J., Blumenthal, J., Helms, M., Luecken, L., Pieper, C., et al. (1997). Psychosocial correlates of job strain in a sample of working women. *Archives of General Psychiatry*, *54*(6), 543–548.

Yoshimasu, K. & The Fukuoka Heart Study Group. (2001). Relation of type A behavior pattern and job-related psychosocial factors to nonfatal myocardial infarction: A case–control study of Japanese male workers and women. *Psychosomatic Medicine*, *63*(5), 797–804.

7 **Okabe S**. Hypothesis—origin of the parietal cell: microorganism? *J Clin Gastroenterol* 1997;**25**(suppl 1):S141–8.
8 **Xia HH**, Talley NJ. Apoptosis in gastric epithelium induced by Helicobacter pylori infection: implications in gastric carcinogenesis. *Am J Gastroenterol* 2001;**96**:16–26.
9 **Neu B**, Randlkofer P, Neuhofer M, *et al.* Helicobacter pylori induces apoptosis of rat gastric parietal cells. *Am J Physiol Gastrointest Liver Physiol* 2002;**283**:G309–18.
10 **Wallace JL**, Cucala M, Mugridge K, *et al.* Secretagogue-specific effects of interleukin-1 on gastric acid secretion. *Am J Physiol* 1991;**261**:G559–64.
11 **Beales IL**, Calam J. Interleukin 1 beta and tumour necrosis factor alpha inhibit acid secretion in cultured rabbit parietal cells by multiple pathways. *Gut* 1998;**42**:227–34.
12 **Wolfe MM**, Nompleggi DJ. Cytokine inhibition of gastric acid secretion—a little goes a long way. *Gastroenterology* 1992;**102**:2177–8.
13 **El-Omar EM**. The importance of interleukin 1beta in Helicobacter pylori associated disease. *Gut* 2001;**48**:743–7.
14 **Schepp W**, Dehne K, Herrmuth H, *et al.* Identification and functional importance of IL-1 receptors on rat parietal cells. *Am J Physiol* 1998;**275**:G1094–105.
15 **Prinz C**, Neumayer N, Mahr S, *et al.* Functional impairment of rat enterochromaffin-like cells by interleukin 1 beta. *Gastroenterology* 1997;**112**:364–75.
16 **Wallmark B**, Stewart HB, Rabon E, *et al.* The catalytic cycle of gastric (H+ K+)-ATPase. *J Biol Chem* 1980;**255**:5313–19.
17 **Sachs G**, Shin JM, Munson K, *et al.* Review article: the control of gastric acid and Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2000;**14**: 1383–401.
18 **Gööz M**, Hammond CE, Larsen K, *et al.* Inhibition of human gastric H(+)-K(+)-ATPase alpha-subunit gene expression by Helicobacter pylori. *Am J Physiol Gastrointest Liver Physiol* 2000;**278**:G981–91.
19 **El-Omar EM**, Oien K, El Nujumi A, *et al.* Helicobacter pylori infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997;**113**:15–24.
20 **Gutierrez O**, Melo M, Segura AM, *et al.* Cure of Helicobacter pylori infection improves gastric acid secretion in patients with corpus gastritis. *Scand J Gastroenterol* 1997;**32**:664–8.
21 **Osawa H**, Kita H, Ohnishi H, *et al.* *Helicobacter pylori* eradication induces marked increase in H^+/K^+-adenosine triphosphatase expression without altering parietal cell number in human gastric mucosa. *Gut* 2006;**55**:152–7.
22 **Furuta T**, Baba S, Takashima M, *et al.* H+/K+-adenosine triphosphatase mRNA in gastric fundic gland mucosa in patients infected with Helicobacter pylori. *Scand J Gastroenterol* 1999;**34**:384–90.

Visceral sensitivity

Can modulating corticotropin releasing hormone receptors alter visceral sensitivity?

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Activation of corticotropin releasing hormone (CRH) receptor 2 (CRH-R2) reduces visceral sensitivity induced by colorectal distension in conscious rats. This finding is relevant to the increased interest in the potential use of therapeutic agents that act on CRH receptors in the treatment of irritable bowel syndrome

Clarifying the adverse effects of stress on bodily function is a crucial paradigm for medical research. Evidence that psychosocial stress aggravates digestive diseases has been accumulating and stress induced exacerbation of symptoms in patients with functional gastrointestinal disorders is well recognised.[1] Corticotropin releasing hormone (CRH), a 41 amino acids peptide produced mainly in the paraventricular nucleus of the hypothalamus, is considered to be a major mediator of the stress response.[2] Indeed, stress is known to induce release of hypothalamic CRH, resulting in pituitary secretion of adrenocorticotropic hormone (ACTH). In addition, stress related activation of CRH receptors has been reported to alter gastrointestinal functions.[3] Moreover, physical or psychological stress is known to delay gastric emptying,[4] accelerate colonic transit,[5] and evoke colonic motility[6] in rats.

Two major G protein coupled receptors for the CRH have been identified, CRH receptor 1 (CRH-R1) and receptor 2 (CRH-R2).[7–9] CRH-R1, which is highly expressed in the anterior pituitary, neocortex, hypothalamus, hippocampus, amygdala, locus coeruleus, and cerebellum, has been reported to mediate stress induced physiological changes, including stimulation of the hypothalamo-pituitary-adrenal axis, elevation of plasma levels of catecholamines, increased colonic motility,[10] and exaggerated stress related behaviour, especially anxiety.[11 12] In addition, stimulation of this receptor is believed to activate adenylate cyclase, an enzyme that catalyses the formation of cyclic AMP (cAMP).[7–9]

We have previously reported increased colonic motility and visceral perception in response to administration of CRH in patients with irritable bowel syndrome (IBS).[13] In addition, earlier studies have indicated that gastrointestinal dysmotility[14] and visceral hypersensitivity[15] are major events in the pathophysiology of IBS. Moreover, patients with IBS have been reported to suffer from a variety of chronic or acute psychiatric conditions, including depression, generalised anxiety, panic, social phobia, and somatisation.[16] Various studies have suggested a relationship between stress induced changes in colonic motility and CRH action in the paraventricular nucleus of the hypothalamus.[17] Accordingly, it has been shown that intracerebroventricular injection of CRH stimulates gastrointestinal motility in a way similar to that induced by stress[18] and that intraperitoneal injection of CRH induces defecation and clustered spike bursts longer than basal spike bursts in rats.[10]

CRH-R1 antagonists have been shown to prevent stress-like gastrointestinal motor responses following central or peripheral injection of CRH.[10] In addition, it has been reported that CRH-R1 deficient mice show impaired response to stress, as indicated by absence of increased ACTH and corticosterone levels following exposure to stress, as well as less pronounced anxiety related behaviour.[11 12] From these findings, it is reasonable to assume that CRH mediates gastrointestinal and behavioural responses to stress via CRH-R1. Actually, in a recent study,[19] we have shown that administration of an α-helical CRH or CRH-R1 antagonist attenuates hippocampal noradrenaline release and reduces the frequency of abdominal contractions induced by acute colorectal distension in rats. We have also shown that the CRH-R1 antagonist used in that study[19] reduced plasma ACTH and anxiety after acute colorectal distension but not after chronic colorectal distension, probably due to habituation. Another important finding of our previous study[19] is that pretreatment with the CRH-R1 antagonist blocked chronic colorectal distension induced increase in rats faecal pellet output. Because the CRH-R1 antagonist used in our previous study[19] is an agent that crosses the blood-brain barrier, both central CRH-R1 and

peripheral CRH-R1 are thought to be responsible for colorectal distension induced sensitisation. Nevertheless, CRH and CRH-R1 in the brain may play a major role in colorectal distension induced anxiety, ACTH release, visceral hypersensitivity, and changes in colonic motility.

Evidence supporting the concept that peripheral CRH and CRH-R1 play important roles in brain-gut sensitisation is increasing. Several studies have identified immunoreactive CRH[20] and urocortin [21] as well as CRH-R1 and CRH-R2 mRNAs in human colonic mucosa.[21] In addition, reverse transcription-polymerase chain reaction (RT-PCR) has revealed expression of CRH-R1 mRNA in both the myenteric and submucosal plexus in the guinea pig.[22] Application of CRH has been shown to evoke depolarising responses associated with elevated excitability in both myenteric and submucosal neurones.[22] On the other hand, peripheral injection of CRH has been reported to induce discrete effects on colonic secretory and motor function, and permeability.[23] We have previously reported that intravenous administration of a non-selective CRH antagonist (α-helical CRH) blunts the exaggerated motility response in the sigmoid colon to electrical stimulation in IBS patients compared with normal subjects.[24] In the same study, we have shown that administration of α-helical CRH induces a significant increase in barostat bag volume in normal subjects but not in IBS patients, and a significant reduction in the ordinate scale of abdominal pain and anxiety evoked by rectal electrical stimulation in IBS patients. However, plasma ACTH and serum cortisol levels were generally not suppressed following administration of α-helical CRH at 10 μg/kg. Although the precise sites of action of α-helical CRH are unknown, we suggested in our previous study that blunting the colonic motor response is mainly due to blockage of peripheral CRH-R1 and that drug anxiolytic or antinociceptive effects are probably based on inhibition of central CRH-R1 via circumventricular organs, which are relatively unprotected by the blood-brain barrier.[24] These findings and concepts, which put in the context of existing preclinical and clinical data, support the testing of new CRH antagonists, particularly potent CRH-R1 antagonists, in IBS and the view that the CRH-R1 receptor is a promising target for the treatment of IBS.[25]

In this issue of *Gut*, however, Million and colleagues[26] provide a new theory for modifying gut sensitivity via CRH-R2 *(see page 172)*. Using RT-PCR, they proved the existence of CRH-R2 in the dorsal root ganglia and spinal cord and hypothesised that CRH-R2 activation may influence visceral pain induced by colorectal distension in conscious rats. By assessing the possible sites and mechanisms of action for CRH-R2 activation, they showed that two repeated colorectal distensions produced visceral sensitisation and phosphorylation of extracellular signal related kinase 1/2 (ERK 1/2) and that intravenous administration of human urocortin 2, a selective CRH-R2 agonist, prevented visceral sensitisation and reduced the second response compared with the first one. Million *et al* also demonstrated that administration of human urocortin 2 dampened distension induced phosphorylation of ERK 1/2 and robust inferior splanchnic afferent spike activity and that treatment with astressin$_2$-B, a CRH-R2 receptor antagonist, reversed the inhibitory effects of human urocortin 2 both in vivo and in vitro.[26]

CRH-R2 is highly expressed in the anterior pituitary, hypothalamus, hippocampus, amygdala, lateral septum, and other peripheral tissues, including the spleen, stomach, and gut.[7–9] Compared with CRH-R1, the functional role of CRH-R2 is relatively obscure. However, recent reports put forward the concept that activation of CRH-R2 signalling pathways may be important to reduce anxiety and stress response.[27 28] There are other functional differences between CRH-R1 and CRH-R2. For example, activation of CRH-R1 causes a proinflammatory response whereas stimulation of CRH-R2 provokes anti-inflammatory changes.[29] In addition, the study by Million and colleagues[26] offers evidence of the contrasting roles of CRH-R1 and CRH-R2 in visceral nociception. While CRH-R1 is involved in the pronociceptive effects of visceral pain, CRH-R2 mediates antinociceptive responses. These findings are supported by a recent report from another group.[30]

Several questions arise from these animal experiments. Do endogenous CRH-R2 ligands such as CRH, urocortin 1, urocortin 2, urocortin 3 (stresscopin), and stresscopin related peptides play an inhibitory role in visceral hypersensitivity in IBS patients? If so, are selective CRH-R1 antagonists more effective for visceral hypersensitivity than non-selective CRH antagonists? Moreover, do agents that block CRH-R2 have any adverse effects on the pathophysiology of IBS? Do CRH-R2 agonists have therapeutic value for IBS and/or allied functional gastrointestinal disorders, even though stress induced inhibition of gastric emptying is mainly mediated via CRH-R2? What are the major steps from the synthesis of cAMP by activated CRH-R2 in the dorsal root ganglia and spinal cord to reduced phosphorylation of ERK 1/2 in the laminae I and II? Thus the disclosed nature of CRH-R2 reported in the present issue of *Gut* brings us an exciting paradigm on research and drug development of the CRH neuropeptide family.

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REFERENCES

1 **Whitehead WE**, Crowell MD, Robinson JC, *et al.* Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared with subjects without bowel dysfunction. *Gut* 1992;**33**:825–30.
2 **Vale W**, Spiess J, Rivier C, *et al.* Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. *Science* 1981;**213**:1394–7.
3 **Tache Y**, Mönnikes H, Rivier J, *et al.* Role of CRF in stress-related alterlations of gastric and colonic motor function. *Ann N Y Acad Sci* 1993;**697**:233–43.
4 **Barquist E**, Zinner M, Rivier J, *et al.* Abdominal surgery-induced delayed gastric emptying in rats: role of CRF and sensory neurons. *Am J Physiol* 1992;**262**:G616–20.
5 **Mönnikes H**, Schmidt BG, Tache Y. Psychological stress-induced accelerated colonic transit in rats involves hypothalamic corticotropin-releasing factor. *Gastroenterology* 1993;**104**:716–23.
6 **Gue M**, Junien JL, Bueno L. Conditioned emotional response in rats enhances colonic motility the central release of corticotropin-releasing factor. *Gastroenterology* 1991;**100**:964–70.
7 **Chen R**, Lewis KA, Perrin MH, *et al.* Expression cloning of a human corticotropin-releasing-factor receptor. *Proc Natl Acad Sci U S A* 1993;**90**:8967–71.
8 **Chang CP**, Pearse RV, O'Connell S, *et al.* Identification of a seven transmembrane helix receptor for corticotropin-releasing factor and sauvagine in mammalian brain. *Neuron* 1993;**11**:1187–95.
9 **Lovenberg TW**, Liaw CW, Grigoriadis DE, *et al.* Cloning and characterization of a functionally distinct corticotropin-releasing factor receptor subtype from rat brain. *Proc Natl Acad Sci U S A* 1995;**92**:836–40.
10 **Maillot C**, Million M, Wei JY, *et al.* Peripheral corticotropin-releasing factor and stress-stimulated colonic motor activity involve type 1 receptor in rats. *Gastroenterology* 2000;**119**:1569–79.
11 **Timpl P**, Spanagel R, Sillaber I, *et al.* Impaired stress response and anxiety in mice lacking a

functional corticotropin-releasing hormone receptor 1. *Nat Genet* 1998;**19**:162–6.
12 **Smith GW**, Aubry JM, Dellu F, *et al.* Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. *Neuron* 1998;**20**:1093–102.
13 **Fukudo S**, Nomura T, Hongo M. Impact of corticotropin-releasing hormone on gastrointestinal motility and adrenocorticotropic hormone in normal controls and patients with irritable bowel syndrome. *Gut* 1998;**428**:45–9.
14 **Kumar D**, Wingate DL. The irritable bowel syndrome: a paroxysmal motor disorder. *Lancet* 1985;**2**:973–7.
15 **Whitehead WE**, Holtkotter B, Enck P, *et al.* Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology* 1990;**98**:1187–92.
16 **Lydiard RB**, Falsetti SA. Experience with anxiety and depression treatment studies: Implications for designing irritable bowel syndrome clinical trials. *Am J Med* 1999;**107**:65–73S.
17 **Bonaz B**, Taché Y. Water-avoidance stress-induced c-Fos expression in the rat brain and stimulation of fecal pellet output: role of corticotropin-releasing factor. *Brain Res* 1994;**641**:21–8.
18 **Lenz HJ**, Burlage M, Raedler A, *et al.* Central nervous system effects of corticotropin-releasing factor on gastrointestinal transit in the rat. *Gastroenterology* 1988;**94**:598–602.
19 **Saito K**, Kasai T, Nagura Y, *et al.* Corticotropin-releasing hormone receptor-1 antagonist blocks brain-gut activation induced by colonic distention in rats. *Gastroenterology* 2005;**129**:1533–43.
20 **Kawahito Y**, Sano H, Kawata M, *et al.* Local secretion of corticotropin-releasing hormone by enterochromaffin cells in human colon. *Gastroenterology* 1994;**106**:859–65.
21 **Muramatsu Y**, Fukushima K, Iino K, *et al.* Urocortin and corticotropin-releasing factor receptor expression in the human colonic mucosa. *Peptides* 2000;**21**:1799–809.
22 **Liu S**, Gao X, Gao N, *et al.* Expression of type 1 corticotropin-releasing factor receptor in the guinea pig enteric nervous system. *J Comp Neurol*, 2005 17, **481**:284–98.
23 **Taché Y**, Perdue MH. Role of peripheral CRF signalling pathways in stress-related alterations of gut motility and mucosal function. *Neurogastroenterol Motil* 2004;**16**(suppl 1):137–42.
24 **Sagami Y**, Shimada Y, Tayama J, *et al.* Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut* 2004;**53**:958–64.
25 **Taché Y**. Corticotropin releasing factor receptor antagonists: potential future therapy in gastroenterology? *Gut* 2004;**53**:919–21.
26 **Million M**, Wang L, Wang Y, *et al.* CRF_2 receptor activation prevents colorectal distension induced visceral pain and spinal ERK 1/2 phosphorylation in rats. *Gut* 2006;**55**:172–81.
27 **Bale TL**, Contarino A, Smith GW, *et al.* Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. *Nat Genet* 2000;**24**:410–14.
28 **Kishimoto T**, Radulovic J, Radulovic M, *et al.* Deletion of crhr2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2. *Nat Genet* 2000;**24**:415–19.
29 **Hsu SY**, Hsueh AJ. Human stresscopin and stresscopin-related peptide are selective ligands for the type 2 corticotropin-releasing hormone receptor. *Nat Med* 2001;**7**:605–11.
30 **Nijsen M**, Ongenae N, Meulemans A, *et al.* Divergent role for CRF1 and CRF2 receptors in the modulation of visceral pain. *Neurogastroenterol Motil* 2005;**17**:423–32.

Incretin

To be or not to be—an incretin or enterogastrone?

M Horowitz, M A Nauck

Glucagon-like peptide 1 does not comfortably fulfil the criterion of a gut derived factor responsible for an enhanced meal related insulin response; it appears logical to add the definition of a "physiological incretin hormone"

Incretin hormones are gut derived peptides that augment the insulin releasing action of hyperglycaemia. In his seminal review, based on the 1978 Claude Bernard lecture, delivered at the European Association for the Study of Diabetes Meeting, Werner Creutzfeldt defined the term incretin as "an endocrine transmitter produced by the gastrointestinal tract which is: (a) released by nutrients, especially carbohydrates and (b) stimulates insulin secretion in the presence of glucose if exogenously infused in amounts not exceeding blood levels achieved after food ingestion".[1] At that time, the best characterised incretin candidate was glucose dependent insulinotropic polypeptide (GIP), although there was evidence that GIP was not the only incretin.[1 3] An incretin role for GIP was established, along the lines of Creutzfeldt's definition,[1] by intravenous infusion in healthy subjects, both alone and in combination with glucose, and demonstrating that the insulinotropic property of GIP was dependent on a permissive rise in blood glucose.[2] Subsequent experiments, performed under more physiological conditions, with plasma GIP and glucose concentrations mimicking the postprandial state, confirmed these observations.[4] That relatively uncomplicated infusion experiments had the capacity to predict the physiological role of GIP with regard to its effects on insulin secretion is testimony to the fact that, metabolically speaking, GIP is apparently devoid of additional actions which have the potential to confound such experiments.[5]

The situation with glucagon-like peptide 1 (GLP-1) is far less straightforward. The GLP-1/glucose infusion experiment results in effects similar to those observed with GIP,[6] and GLP-1, accordingly, fulfils the definition of an incretin hormone, as put forward by Creutzfeldt.[1] However, studies which have evaluated the effects of GLP-1 on the metabolic response to a meal, by infusing physiological or pharmacological amounts of GLP-1,[7] or interfering with endogenous GLP-1 action with the well characterised GLP-1 antagonist exendin(9–39),[8–10] have revealed a complex pattern of GLP-1 actions. In particular, as a result of its effect on slowing gastric emptying substantially, exogenous GLP-1 attenuates the postprandial rise in glycaemia, leading to lesser substrate (glucose) mediated insulin secretion and an overall reduction, rather than an increase, in the insulin secretory response to a meal.[7 11 12] In other words, inhibition of gastric emptying by exogenous GLP-1 outweighs its direct insulinotropic effects. This was highlighted in a recent study demonstrating that intravenous erythromycin, as a result of its prokinetic properties, abolishes the deceleration of gastric emptying induced by exogenous GLP-1 in healthy subjects and that this is associated with a marked reduction in its glucose lowering effect.[12] Furthermore, the GLP-1 antagonist exendin(9–39) increases, rather than lowers, the insulin response to a meal.[13] Based on these observations it is clear that GLP-1 does not comfortably fulfil the criterion of a gut derived factor responsible for an enhanced meal related insulin response; furthermore, it appears logical to add the definition of a "physiological incretin hormone" to that provided by Creutzfeldt,[1] and assigning such a role to GLP-1 appears inappropriate based on current data.[11]

In their important study in the current issue of *Gut*, Schirra and colleagues[14] have introduced a new approach to evaluation of the incretin role of GLP-1 in healthy subjects *(see page 243)*. They used intraduodenal administration

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SHORT REPORT

Abnormal relationship between dissociation and hypnotic susceptibility in irritable bowel syndrome

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort which is associated with changes in stool frequency and/or form [1]. Standard medical treatment is of benefit to only about 50% of patients with IBS. In contrast, hypnotherapy has been shown to be very effective in the treatment of IBS in up to 80% of patients [2]. However, few reports are available on the relationship between IBS and hypnotic susceptibility. The previous studies demonstrated that a dissociative tendency toward time, location, and sense of self increased hypnotic susceptibility [3]. The present study was therefore designed to test the hypothesis that a dissociative tendency can account for the link between IBS and hypnotic susceptibility.

Material and methods

One hundred and eighty-seven male volunteers were recruited from universities in Sendai and screened with the dissociative experiences scale (DES) [3]. Men were enrolled to preclude the possible influence of the menstrual cycle on gastrointestinal symptoms. The DES consists of 28 questions to assess dissociative experiences [3]. Experiences were rated on a scale of 0% (never have the experience) to 100% (always have the experience). The averaged DES was 9.7 ± 8.5. Individuals with the mean DES score above the 80 percentile were considered as "high dissociative subjects" ($n = 39$, mean 22.1 ± 8.4), while those with a score of below the 30 percentile were considered "low dissociative subjects" ($n = 44$, mean 1.7 ± 0.8). These high/low cut-offs have been used in previous research [4]. IBS status was diagnosed using the Rome II criteria [1] and 39 subjects out of 187 individuals had IBS. As a result, the following subjects were identified; 18 healthy-high dissociative, 19 healthy-low dissociative, 12 IBS-high dissociative and 8 IBS-low dissociative. Group mean ages were 20.1 ± 2.3, 20.4 ± 1.8, 20.1 ± 2.0 and 20.5 ± 1.6, respectively. The subjects completed the Japanese version of the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS-A) [5] in a temperature-controlled, quiet room. The Tohoku University Ethics Committee approved the experimental procedure. All volunteers gave written informed consent before participation. Data were expressed as means $\pm$ SE and were analyzed with the SPSS software (version 10.0). The Mann-Whitney U-test, two-way analysis of variance (ANOVA), and *post hoc* test were used and a p-value of less than 0.05 (ANOVA) and a p-value of less than 0.01 (*post hoc*) were considered as significant.

Results

There was no significant difference in DES score between healthy controls (10.7 ± 7.4) and IBS subjects (11.0 ± 7.6) ($z = -1.66$, $p > 0.05$). Two-way ANOVA of the HGSHS-A revealed significant interaction between groups (controls versus IBS subjects) and dissociative status (high DES versus low DES), ($F(1.53) = 4.84$, $p < 0.05$, Figure 1). The *post hoc* test indicated that high dissociative controls have significantly higher HGSHS-A than low dissociative controls ($p < 0.01$). However, high dissociative IBS subjects have similar HGSHS-A to low dissociative IBS subjects ($p > 0.05$) and scored

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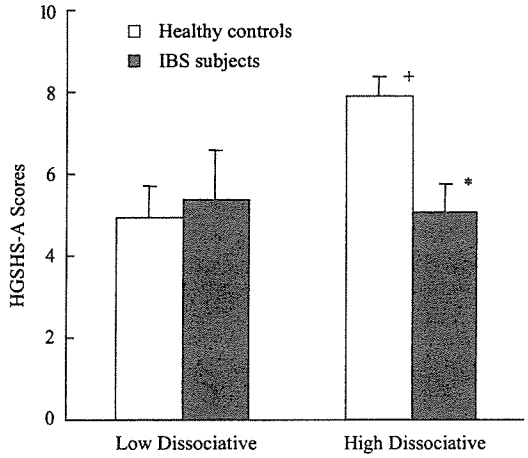

Figure 1. Differences in Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS-A) among four groups. Data are expressed as means ± SE. □ = healthy controls; ■ = IBS (irritable bowel syndrome) subjects; Low Dissociative = subjects with low DES; High Dissociative = subjects with high DES. Two-way analysis of variance (ANOVA), interaction ($p < 0.05$) + $p < 0.01$: versus healthy – low dissociative subjects, *$p < 0.01$: versus healthy – high dissociative subjects, *post hoc* test.

significantly lower HGSHS-A than high dissociative controls ($p < 0.01$).

Comment

The results of the present study refuted our initial hypothesis that a dissociative tendency could account for the link between IBS and hypnotic susceptibility. On the contrary, IBS subjects failed to demonstrate a normal association between dissociative tendency and hypnotic susceptibility that has been reported in studies of non-IBS subjects. This study is limited by only having included male subjects but provides basic information for neuroimaging research. A recent study with functional magnetic resonance imaging revealed that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions and was associated with increased activity during anticipation of pain in the prefrontal cortex, providing evidence that suggestion alters the experience of pain [6]. IBS patients are known to have more activation of dorsolateral prefrontal cortex blood flow to colorectal distension [1]. Therefore, individuals with IBS may have disturbed pain-modulating brain processing in the cortical levels, and this characteristic may account for the lack of association between a dissociative tendency and hypnotic susceptibility.

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References

[1] Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE. Rome II: the functional gastrointestinal disorders, 2nd ed. McLean: Degnon Associates; 2000. pp 1–432.

[2] Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. Lancet 1984;2:1232–4.

[3] Bernsein EM, Putnam FW. Development, reliability, and validity of a dissociation scale. J Nervous Mental Dis 1986; 174:727–35.

[4] Engel CC, Walker EA, Katon WJ. Factors related to dissociation among patients with gastrointestinal complaints. J Psychosom Res 1996;40:643–53.

[5] Shor RE, Orne EC. Harvard Group Scale of Hypnotic Susceptibility, Form A. Palo Alto, CA: Consulting Psychologists Press; 1962.

[6] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Dvidson RJ, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 2004;303: 1162–7.

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Rapid communication

Validation of the Japanese version of the Rome II modular questionnaire and irritable bowel syndrome severity index

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Background. Instruments for measuring the presence and severity of specific irritable bowel syndrome (IBS) symptoms, comparable to those used in Western countries, have been lacking in Japan. The aim of this study was to develop, validate, and confirm the reliability of the Japanese version of the Rome II modular questionnaire for IBS (RIIMQ-J) and the IBS severity index (IBSSI-J). ***Methods.*** Forty-nine patients in the university hospital with chronic or recurrent abdominal pain and discomfort and/or altered bowel habits were enrolled. With Rome II criteria, 27 patients were diagnosed as having IBS, and the other 22 patients were evaluated as having other functional bowel disorders (FBDs). The English versions of RIIMQ and IBSSI were translated into Japanese. After back-translation and approval of the questionnaire, subjects completed both questionnaires twice within 14 days. ***Results.*** Cronbach's alpha of the RIIMQ-J was high (0.72). The sensitivity of RIIMQ-J for the diagnosis of IBS was also high (89%). The specificity of RIIMQ-J for denial of IBS among patients with other FBD was satisfactory (73%). The IBSSI-J showed high internal consistency (0.69) and reproducibility (intraclass correlation coefficient, 0.86, $P < 0.001$). ***Conclusions.*** The RIIMQ-J and IBSSI-J are valid, reliable, and appropriate instruments for detecting and assessing the severity of IBS status in Japanese patients.

Key words: irritable bowel syndrome (IBS), Rome II modular questionnaire (RIIMQ), IBS severity index (IBSSI), validation study.

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Introduction

Irritable bowel syndrome (IBS) is a very common chronic gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits without major organic disease by routine gastroenterological examination.[1] Rome II diagnostic criteria based on subjective gastrointestinal (GI) complaints are the most widely used criteria for diagnosing IBS.[2,3] On the basis of these criteria, the Rome II modular questionnaire (RIIMQ) was developed,[4] and it has been used for epidemiological studies in Western countries.[5,6] Moreover, instruments for determining the severity of IBS are useful for clinical trials and epidemiological surveys.[7–9]

Instruments comparable to those used in the Western countries for measuring the presence and severity of specific IBS symptoms have been lacking in Japan. To make cross-cultural comparisons possible, it is indispensable to develop common diagnostic and severity measures for IBS. The aim of this study was to develop, validate, and confirm the reliability of Japanese versions of the RIIMQ (RIIMQ-J) for IBS and the IBS severity index.

Subjects and methods

Fifty-nine consecutive patients who visited the department of psychosomatic medicine in Tohoku University Hospital in Sendai, Japan, with chronic or recurrent abdominal pain and discomfort and/or altered bowel habits were enrolled as having a functional bowel disorder (FBD).[2,7] Among them, 49 patients (27 women and 22 men) filled out the questionnaires completely twice within 14 days, between July and December 2004.

Patients with IBS ($n = 27$) were diagnosed with Rome II criteria.[2,4] In brief, these criteria are as follows: at least 12 weeks, which need not be consecutive, during the

preceding 12 months of abdominal discomfort or pain that has two of the following three features: (1) relieved with defecation; (2) onset associated with a change in stool frequency; and/or (3) onset associated with a change in the form (appearance) of the stool. The following symptoms cumulatively support the diagnosis of IBS: fewer than three bowel movements a week; more than three bowel movements a day; hard or lumpy stools; loose (mushy) or watery stools; straining during a bowel movement; urgency (having to rush to have a bowel movement); feeling of incomplete bowel movement; passing mucus (white material) during a bowel movement; and abdominal fullness, bloating or swelling.

Those patients without IBS ($n = 22$) were considered to have another FBD. All subjects were Japanese, and they did not have any organic GI diseases or any other severe physical or psychiatric complications. The rationale for selecting the subjects for this study was as follows. First, Tohoku University Hospital is a tertiary hospital visited by typical IBS patients. Second, detecting the difference between IBS and other FBDs is a strict discrimination problem that is suitable for the development of screening and grading tools. The mean age ± SE of the participants was 38 ± 2 years (19–79 years). Among them, 24 were married, 14 were single and living with family, 10 were single and living alone, and 1 was divorced. Written informed consent was obtained from all the participants. This study was approved by the Ethics Committee of Tohoku University School of Medicine.

RIIMQ was developed in English as a diagnostic instrument for functional GI disorders according to the Rome II diagnostic criteria.[4] For IBS diagnosis, four items related to major IBS symptoms and 11 supporting items on bowel movements are used.[4,5]

The IBS severity index (IBSSI) was developed and is widely used in Western countries to assess the severity of lower GI symptoms and the degree to which the quality of life is impaired by IBS.[8] This instrument has five items, and the total score can range from 0 to 500. The IBSSI scores abdominal pain, abdominal distension, bowel movements, and the quality of life. In the original, English version, IBS is graded as mild (75–174), moderate (175–299), or severe (300–500) on the basis of clinical observations of IBS patients.[8] In addition, to assess the severity of abdominal pain, subjects are asked if they have had pain in their abdomen all the time (continuously) or most of the time (nearly continuously) during the previous 6 months.

The two Japanese coresearchers translated the English version of RIIMQ for IBS and the IBSSI into Japanese. After the descriptions of each item had been discussed with specialists, the Japanese versions of the instruments were then counter-translated into English by a native speaker of English at Tohoku University. These back-translated versions were sent to the Rome Committee, compared with the original versions, and discussed to confirm that the Japanese-translated versions were comparable to the English versions of RIIMQ and IBSSI. Then, the Japanese versions of these instruments, RIIMQ-J and IBSSI-J, were approved for use by the authors of the original English versions.[4,8]

The χ-squared test was used to assess the agreement between a positive diagnosis by RIIMQ-J and a clinical diagnosis, as assessed by two of the authors (SF and MK), who each have had been physicians at the functional GI disorder clinic at Tohoku University Hospital for more than 10 years. Simple regression analysis was used to confirm the test–retest reliability. Cronbach's alpha was calculated to assess internal consistency. Logistic regression analysis was used to determine the relationships among the severity scores, age, sex, and marital status.

Results

The RIIMQ-J for IBS demonstrated relatively high reproducibility and high internal consistency (Cronbach's alpha, 0.72). The sensitivity of RIIMQ-J for the diagnosis of IBS was also high (89%, Table 1). The specificity of RIIMQ-J for denial of IBS among the patients with another FBD was also satisfactory (73%).

The IBSSI-J also showed relatively high internal consistency (0.69) and high reproducibility (intraclass correlation coefficient, 0.86; $P < 0.001$). IBS patients with a positive RIIMQ-J judgment received signifi-

Table 1. Agreement between the clinical diagnosis of IBS and RIIMQ-J

		IBS diagnosed with RIIMQ-J		
		Positive	Negative	Total
IBS diagnosed by physicians	Positive	24 (89%)	3 (11%)	27 (100%)
	Negative	6 (27%)	16 (73%)	22 (100%)
	Total	30	19	49

IBS, irritable bowel syndrome; RIIMQ-J, Japanese version of Rome II modular questionnaire

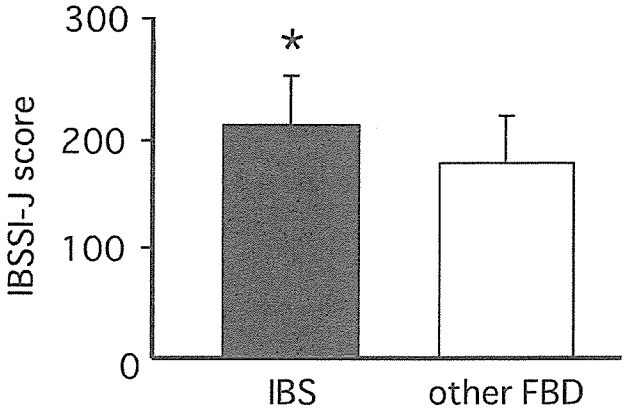

Fig. 1. Scores on the Japanese version of IBS severity index (*IBSSI-J*) between IBS patients and patients with another functional bowel disorder (*FBD*). Data are shown as means ± SE; $^*P < 0.01$

cantly higher IBSSI-J scores than the patients with another FBD (250 ± 17 vs. 172 ± 21; $P < 0.01$; Fig. 1). Thirty patients with IBS diagnosed by the RIIMQ-J were graded as having mild (20%), moderate (43%), or severe (37%) symptoms on the basis of their IBSSI-J scores, thus showing a similar distribution of severity as patients graded with the English original version.[8] Moreover, patients who had had continuous or nearly continuous abdominal pain during the previous 6 months (n = 8) received higher IBSSI-J scores than subjects who had not (352 ± 28 vs. 194 ± 13; $P < 0.001$). Age, sex, level of education, and marital status did not affect the IBSSI-J score.

Discussion

We confirmed the validity and reliability of the RIIMQ-J and IBSSI-J according to a standard method. A previous study from our laboratory demonstrated that the prevalence of IBS in Japan is similar to that in the United States, but there are no differences between sexes.[10] The questionnaire used in the previous study[10] was based on Rome II criteria but differed from the RIIMQ. In addition, the surveyed population comprised laborers seeking a health check.[10] The instruments of the present study, on the other hand, allow us to assess the presence and severity of IBS and other functional bowel disorders in a large Japanese population in a way comparable to that used in Western countries.

In an earlier report from the United States, total agreement between a clinical diagnosis of IBS and the RIIMQ was 63% for gastroenterologists and 57% for primary care (PC) physicians.[11] In a report from Norway, the agreement rate was 58% for PC physicians.[12] The sensitivity of RIIMQ-J in our study (89%) was much higher than that in the earlier studies. This difference between those studies and the present study may depend on differences in subjects and physicians. The subjects in this study had gone to a tertiary care hospital for consultation, whereas the subjects in the other studies had consulted general practitioners.[11,12] In contrast, the specificity of RIIMQ-J for denial of IBS among patients with another FBD (73%) was not as high as the sensitivity. Thus, the false positive rate of RIIMQ-J for misdiagnosing IBS among patients with another FBD was 27%. This is a limitation of the questionnaire, but it is a reasonable result because RIIMQ was designed to screen for IBS symptoms, not to determine a diagnosis of IBS.

In the present study, 30 patients with IBS diagnosed by the RIIMQ-J were assessed as having mild (20%), moderate (43%), or severe (37%) in accordance with the reported grading system.[8] The distribution among grades in our sample was similar to that among patients assessed with the original English version at a university hospital in the UK.[8] Moreover, reasonably, IBS patients scored higher on the IBSSI-J than patients with another FBD. Although we did not use IBSSI-J to assess healthy control subjects, the high consistency, high reproducibility, and comparability of our results with those in earlier reports support the usefulness of this questionnaire in Japan.

In conclusion, we developed the RIIMQ-J and IBSSI-J, which are reliable and clinically appropriate instruments for diagnosing and assessing the severity of IBS in Japanese patients. These instruments will be useful tools for cross-cultural comparison studies of functional GI disorders.

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References

1. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology 1997;112:2120–37.
2. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999;45(Suppl II):II43–7.
3. Boyce PM, Koloski NA, Talley NJ. Irritable bowel syndrome according to varying diagnostic criteria: are the new Rome II criteria unnecessarily restrictive for research and practice? Am J Gastroenterol 2000;95:3176–83.
4. Drossman DA, Talley NJ, Whitehead WE, Corazziari E. Research diagnostic questions for functional gastrointestinal

disorders: Rome II modular questionnaire: investigations and respondent forms. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, editors. Rome II: the functional gastrointestinal disorders. 2nd ed. McLean, VA: Degnon Associates; 2000. p. 669–714.
5. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. Dig Dis Sci 2002;47:225–35.
6. Parry SD, Stansfield R, Jelley D, Gregory W, Phillips E, Barton JR, et al. Does bacterial gastroenteritis predispose people to functional gastrointestinal disorders? A prospective, community-based, case–control study. Am J Gastroenterol 2003; 98:1970–5.
7. Drossman DA, Li Z, Toner BB, Diamant NE, Creed FH, Thompson D, et al. Functional bowel disorders. A multicenter comparison of health status and development of illness severity index. Dig Dis Sci 1995;40:986–95.
8. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395–402.
9. Svedlund J, Sjodin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33:129–34.
10. Kanazawa M, Endo Y, Whitehead WE, Kano M, Hongo M, Fukudo S. Patients and nonconsulters with irritable bowel syndrome reporting a parental history of bowel problems have more impaired psychological distress. Dig Dis Sci 2004;49:1046–53.
11. Whitehead WE, Palsson OS, Levy RL, Feld AD, Von Korff M, Drossman DA, et al. Agreement of Rome criteria with clinical diagnosis of irritable bowel syndrome (IBS). Gastroenterology 2003;124:A397.
12. Vandvik PO, Aabakken L, Farup PG. Diagnosing irritable bowel syndrome: poor agreement between general practitioners and the Rome II criteria. Scand J Gastroenterol 2004;39:448–53.