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Novel associations with dyspepsia: A community based study of familial aggregation, sleep dysfunction and somatization

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Abstract

Background—Dyspepsia is common and the majority of patients have functional dyspepsia; however, potential risk factors are unclear with conflicting results in the literature. Although several risk factors have been evaluated previously, this knowledge has not lead to more effective management.

Aim—To assess potential novel risk factors for dyspepsia in both a cross sectional and a nested case control study among a randomly selected community based cohort.

Methods—A valid questionnaire was mailed to a random sample of Olmsted County, MN residents (n=659 responders; 133 had dyspepsia). In a nested case-control study, dyspeptic patients (n=52) and healthy controls (n=40) identified among community respondents completed further questionnaires on diet.

Results—Independent risk factors for dyspepsia adjusted for age, sex, body mass index and anti-secretory therapy were a positive family history of abdominal pain (OR=4.7, 95% CI 1.5, 14.9, p=0.008) and indigestion (OR=3.4., 95% CI 1.0, 11.5, p=0.04) difficulty falling asleep (OR=8.2, 95% CI (2.2–31.5, p=0.002), poor sleep associated with worsening symptoms (OR=15.9, 95% CI (2.0–124.9, p=0.009) and a high somatic symptom checklist score (OR=5.6, 95% CI (1.5–20.7, p=0.01). Diet including total calories (kcalories/day) and total protein, carbohydrate and fat intake (grams/day) was not significantly associated with dyspepsia

Conclusions—Familial aggregation raises the possibility of a genetic component although shared environmental factors need to be considered. Sleep dysfunction and somatization suggests a primary psychological component.

Introduction

Dyspepsia has been defined as chronic or recurrent pain or discomfort centered in the upper abdomen [1]. Estimates of the prevalence of dyspepsia in the community have varied among studies [2], in large part because of differences in the definitions used. The annual prevalence of recurrent abdominal pain or discomfort in the United States and other western countries is approximately 25% [3, 4]. Notably, the number of subjects who develop dyspepsia appears to be matched by a similar number of subjects who lose their symptoms,

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so the prevalence remains stable from year to year [5, 6]. Despite the high prevalence of functional dyspepsia both in the community and in the clinic population, our understanding of the pathophysiology of the disorder is very limited [3]. A number of potential risk factors (*Helicobacter pylori*, diet, stress, anxiety, depression and abuse) have been evaluated, but few of these studies have been conclusive [7]. We aimed to assess potential (including novel) risk factors for dyspepsia in both a cross sectional and a nested case control study among a randomly selected community based cohorts.

Methods

Epidemiology

The Olmsted county population has approximately 124, 277 people (in 2000) and 89 % are white. Sociodemographically the population is similar to US white population [8]. The Rochester Epidemiology Project (REP) is a medical records linkage system which records all care provided to Olmsted County, Minnesota residents. Prior studies have determined that 96% of all county residents have had a medical encounter over any 4 year period [8]. Hence, an enumeration of the County population is possible for population-based research. The REP has been used to perform a series of population based studies to gather information on gastrointestinal symptoms in the community [3].

Study design

Phase 1

Survey Methods: A revised Talley Bowel Disease Questionnaire (BDQ) was developed using previously validated individual question items. The questionnaire was initially developed at Mayo Clinic in 1988 [8] and consists of 71 separate items that were individually tested for reliability using a test retest method and concurrent validity by comparison with a physician interview. Additional questions were developed for further measurement of dyspepsia and familial aggregation in 1993 [9, 10]. Because the symptom items were tested individually, subsequent questionnaires have used selected questions in the instruments. The Modified Bowel Disease Questionnaire (MBDQ) contains all the symptom items required for identifying symptoms of dyspepsia and its subtypes, as well as symptoms of irritable bowel syndrome, gastroesophageal reflux, and other gastrointestinal symptoms. At the end of the survey, a somatic symptoms checklist (SCC) was included, which measures the frequency and severity of non-GI complaints [11].

Two versions of the MBDQ were used in the survey portion of this study. The long MBDQ developed for the study has 66 primary questions and an additional 38 questions in drop down boxes. It was 14 pages long with questions organized into 15 sections: indigestion, upper abdominal symptoms, nausea and vomiting, early satiety and bloating, heartburn, acid regurgitation, difficulty swallowing, chest pain, lower abdominal pain and bowel habits. Risk factors evaluated included family history, insomnia, body mass index (BMI), medication history, gastroesophageal reflux disease (GERD), irritable bowel syndrome, gender, age and somatic symptoms.

A shorter version of this survey was developed with 36 primary questions (identical to long survey) and an additional 15 questions in drop down boxes. This survey instrument was 8 pages in length and the questions are organized in 10 sections. The sections corresponding to dysphagia, chest pain, vital statistics, family history and insomnia that were present in the long survey were omitted.

Previous community based surveys by the authors had drawn stratified random samples of Olmsted County MN residents yielding a combined cohort of 9,327 subjects that had been

mailed one or more surveys [12–15]. For this study the investigators drew an age (5 year interval) and gender (equal number of men and women) stratified random sample of 1500 residents from this cohort. The sample was checked for authorization to use medical records and willingness to be contacted for research. Those subjects who declined involvement in research, had moved out of Olmsted County, or were deceased were not included. No one was excluded on the basis of race.

The long survey was to be mailed to an initial sub-sample of 500 of the 1500 subjects selected for this study, and the remaining 1000 subjects were to be mailed the shorter version of the survey. After all exclusions were applied to the sample of 1500 people, the sample size left was 1461 persons (484 were to be mailed the long survey and 880 the shorter version) [3].

Each eligible subject was mailed a cover letter and questionnaire. The cover letter asked for participation or return of the cover letter indicating refusal to participate. Non responders were sent a second mailing after one month. No further attempt to contact after the second mailing was made, as required by the Mayo Clinic Institutional Review Board. Using answers from the long and short questions, individuals were identified as meeting symptom criteria for functional dyspepsia or not.

Phase II

Risk factors for Dyspepsia in a Nested Case Control Study: A review of medical records for each of those individuals identified by the questionnaire as dyspeptic or healthy control was performed and those who did not meet the criteria were excluded. Exclusion criteria were as follows: pregnancy or breast feeding; history of abdominal surgery other than appendectomy or hysterectomy, caesarian section or tubal ligation; history of eating disorder, gastrointestinal disease or systemic disease or use of medications that could cause gastrointestinal side effects (e.g. non steroidal anti-inflammatory drugs). Those who met criteria (n = 162) were invited to Mayo Clinic GCRC for a physician interview to complete questionnaires (MBDQ, food frequency questionnaire and the SCL 90) and to have blood drawn for *H. pylori*. Only the individuals invited to the GCRC received remuneration. Physician interviews were done at this time to verify symptom status. A total of 92 out of 162 participated in phase II. A total of 13 of these 92 (14%) had an EGD prior to the survey. 10/13 (77 %) could be categorized as NUD.

Definitions

The definition for dyspepsia in this study was any individuals that answered YES to the question, in the last year have you had troublesome upper abdominal, stomach or belly symptoms and YES to the question, have you had the same most troublesome symptom for at least 25% of the time. In phase I this could be defined in 221 of the 224 patients that completed the long survey: 3 participants did not complete the above questions. In phase II, of the 92 participants, 35 (cases) met the definition of dyspepsia and 57 were asymptomatic (controls).

Irritable bowel syndrome (IBS) was defined using Rome II criteria. IBS was defined as a combination of frequent abdominal pain and an altered bowel habit. The altered bowel habit had to have two or more of the following three characteristics: 1) relieved by defecation; 2) associated with a change in stool frequency (either more or fewer BM's); or 3) associated with a change in stool form (either looser or harder).

Measurement of Risk Factors

Health and medications—Previous hospital diagnosis of IBS, GERD, dyspepsia, constipation, diarrhea, infection and cancer was assessed for responses to the questionnaire as well as current symptomatology including indigestion, upper abdominal symptoms, nausea and vomiting, early satiety and bloating, heartburn, acid regurgitation, difficulty swallowing, chest pain, lower abdominal pain and bowel habits over the last year. Medication including aspirin, acetaminophen, antispasmodics, anti-secretory drugs, and laxatives were assessed from the questionnaire to determine any association between dyspepsia with certain medications.

Food Frequency Questionnaire—The food frequency questionnaire (the Block 2000 Modification of the Block/NCI Health Habits and History Questionnaire) was used in this study. This questionnaire includes food representing at least 90% of the total US consumption of at least 18 major nutrients. It asks detailed information about the frequency of use and common serving for each item of fruits and juices, breakfast foods, vegetables, meats, bread, snack foods, spreads, dairy products, sweets and beverages. It also collects information about the use of supplemental vitamins [16].

***H. pylori* testing**—Individuals in phase II had blood drawn for *H. pylori* serology, and the results have been reported elsewhere [3]. Only 15 (16%) tested positive for *H. pylori*.

Family History—Family history of indigestion, abdominal pain, GERD and bowel problems were assessed from the questionnaire.

Statistical analysis

In phase 1, the odds for reporting symptoms consistent with dyspepsia were estimated for each potential risk factor using logistic regression models adjusting for age, gender, BMI and anti-secretory therapy. A backwards elimination method was used to identify independent risk factors (forcing age, gender and BMI to be included in the final model). In phase 2, logistic regression models were used to estimate the odds ratios (and 95% CIs) for each risk factor, again adjusted for age gender and BMI, but no multiple variable model building was undertaken. All p values calculated were two tailed: the alpha level of significance was set at 0.05. Statistical analysis was carried out with the software package SAS.

Results

Response rate

The long survey was mailed to a random sample of 466 of the 1346 sample. There were 224 who completed the long survey, 66 people refused to participate, 158 did not respond to our mailings, and 18 people were excluded secondary to having moved out of Olmsted County. The response to the long version was 48% [3]. The shortened survey was mailed to 880 people: 435 completed the questionnaire, 119 refused to participate and 319 did not respond. The response rate to the short questionnaire was 49%. Thus, the overall response for both the long and short questionnaire was 49%. Of the 659 surveyed, 133 (20%) met criteria for dyspepsia and 11 subjects could not be classified.

Demographics of responders

Phase 1 respondents to the mailed questionnaire were 52% women with a median age of 61 yrs. (interquartile range, 50–71 years). There was no significant associations between gender

distribution and participation (responders). For those whose race was disclosed 97% were Caucasian, and 1% each were Asian, African American, or other.

Risk factors

In the phase 1 univariate analysis, those individuals with a positive family history had an increased odds for reporting dyspepsia relative to those that had a negative family history ($p<0.001$) (table 1). As shown in Table 1, the increased odds were significant in those with a positive family history of indigestion and abdominal pain as well as those with a family history of GERD or bowel problems.

Insomnia was a risk factor for dyspepsia with an increased odds for reporting dyspepsia in subjects complaining of sleep dysfunction relative to those not ($p=0.006$). Specifically, 31% of subjects complaining of waking up not feeling rested reported dyspepsia versus 16% of participants who woke up rested. Among subjects reporting difficulty falling asleep, 38 % reported dyspepsia versus 18% who did not have any difficulty ($p= 0.01$). Among those subjects reporting worsening bowel problems associated with worsening sleep problems, 79% met criteria for dyspepsia while 20% without worsening sleep/bowel problems did not report dyspepsia ($p <0.001$). Somatic symptom scores above the median were also a risk factor for dyspepsia.

Antacids ($p=0.003$), H2 antagonists ($p=0.004$) and proton pump inhibitors ($p<0.001$) were associated with dyspepsia as expected. In addition, acetaminophen use was univariately associated with dyspepsia. Overall, 34% of participants who were taking acetaminophen complained of dyspepsia vs. 66% without dyspepsia, implying a protective effect. Other potential risk factors including gender, age group, BMI, race, marital status, aspirin, alcohol and nicotine use were not found to be univariately significant risk factors (Table 1).

In the multiple variable model, family history of indigestion ($p=0.048$) and family history of abdominal pain ($p=0.008$), difficulty sleeping ($p=0.002$), worsening bowel problems associated with worsening sleep problems ($p=0.009$) and somatic symptom score above the median ($p=0.01$) were independently significant, adjusting for H2 receptor antagonists and proton pump inhibitors as well as age and gender. Acetaminophen use was not associated but aspirin became significant in the multiple variable model.

In phase II, the dietary characteristics in particular total calories (kcalories/day) and total protein, carbohydrate, fat intake (grams/day) were not significantly associated with dyspepsia (Table 2). Table 3 shows the dietary intake of cases versus controls. Cases consumed a mean of 1610.9 $\pm$ 705.2 kilocalories, and this was not statistically different from controls who consumed a mean of 1558.8 $\pm$ 643.5 kilocalorie ($p = 0.86$). Cases and controls consumed similar amounts of mean, total protein, (68.9 $\pm$ 31.0 versus 67.6 $\pm$ 26.5, $p = 0.76$), total carbohydrate (189.7 $\pm$ 71.2 versus 192.4 $\pm$ 78.6 $p = 0.41$), and total fat intake grams/day (62.9 $\pm$ 37.3 versus 57.2 $\pm$ 31.5, $p= 0.72$). Cases and controls consumed similar amounts protein, carbohydrate and fat percentages as part of the total caloric intake.

Discussion

Dyspepsia in the community is highly prevalent but the underlying casual pathways remain unknown. In this study, data from a previous study [3] was re-analyzed to search for possible etiological factors for the development of dyspepsia in a randomly selected community based cohort with unexplained dyspepsia and healthy controls. We assume that the vast majority of the subjects with dyspepsia in the present cohort had functional dyspepsia, as most were *H. pylori* negative and clinically did not have obviously structural

disease. The risk factors identified in this study included family clustering, insomnia and somatization.

An association between sleep disturbances and functional GI disorders has been reported by several investigators [17, 18] and this work complements those observations. Conceivably any abdominal pain could explain the sleep disturbances if it causes patients difficulty going to sleep or awakens them from sleep. Conversely, a specific sleep disturbance might predispose to functional bowel disturbance [17]. For example, a prolonged disruption of Stage 4 or slow wave (deep) sleep in healthy subjects resulted in the emergence of gastrointestinal symptoms such as nausea, abdominal cramping and somatic symptoms that included musculoskeletal complaints and fatigue [19]. Changed sleep patterns have also been associated with altered nocturnal duodenal activity, which in turn, occurs in a subset with functional dyspepsia [20]. There are other possible explanations for the observed increased sleep disturbance in dyspeptic patients. Dyspeptic symptoms in a fraction of patients with unexplained dyspepsia may actually represent unrecognized gastroesophageal reflux disease and CNS arousal from esophageal chemoreceptor stimulation by nocturnal acid reflux events [21]. Poor subjective sleep quality is not mirrored by objective polysomnographic monitoring in IBS suggesting that altered sleep perception involves an exaggerated response to normal internal or external stimuli [22].

A history of abdominal pain or bowel problems in first degree relatives is known to be strongly associated with IBS, but much less data are available for dyspepsia [23]. In this study we observed an increased odds of dyspepsia in those with a positive family history of indigestion or abdominal pain, but not bowel problems or GERD after adjusting for confounding. Whether the familial associations represent reporting bias, similar exposures in a shared environment, heightened familial awareness of GI symptoms or genetic factors in dyspepsia remains to be determined [10]. Same sex twins enrolled in an Australian twin registry completed a structured interview that included questions related to functional bowel symptoms. This study suggested there is a substantial genetic component of functional bowel disorders and that the results seemed unlikely to be explained by bias [24]. On the other hand, another US twin study failed to find evidence for a genetic component in dyspepsia [25]. The key genes involved in the development of dyspepsia remain to be identified assuming a genetic link exists. Holtmann et al observed a significant link between GN β 3 (C285T) CC genotype and functional dyspepsia (OR=2.2, 95% CI-1.4–3.3) [26]. These results appear to be confirmed in a study by Camilleri et al which reported that meal-unrelated dyspepsia in a U.S. community study is associated with the homozygous 825T or C alleles of GN β 3 protein [27]. In contrast, Van Lelyveld et al reported that functional dyspepsia patients displayed a higher prevalence of the T allele of GN β 3 C825T polymorphism compared to healthy controls (OR=1.60, 95 % CI 1.03–2.49, P=0.038) [28]. Further studies on genetic polymorphisms and the relationship with functional dyspepsia are required.

Patients with functional dyspepsia frequently report that symptoms are related to, exacerbated by food, particularly rich and fatty foods and that they are able to tolerate only small amounts of food at one meal [16]. Meal ingestion is associated with diverse changes in gastrointestinal function, and potential pathophysiological mechanisms include abnormally delayed or accelerated gastric emptying, disturbed intragastric meal distribution associated with impaired proximal gastric accommodation and increased antral filling, gastric or small intestinal hypersensitivity to mechanical and/or chemical/nutrient stimuli, gastric hypersecretion, and abnormalities in secretion of, and/or sensitivity to gastrointestinal peptides [29]. Our results suggest that specific food ingestion is not a major mechanism inducing dyspepsia in the community, but prospective studies of dietary intake are needed to

further elucidate the nutritional components of food substances that may aggravate or cause dyspepsia [30].

We observed that acetaminophen was not associated with dyspepsia, and may even be protective although this was not significant. Acetaminophen use (3 tablets/week vs. none) has been linked to dyspepsia with an odds ratio of 2.2 (95% CI 1.5, 3.1) but on adjusting for non-gastrointestinal somatic symptoms, acetaminophen was no longer a significant risk factor in the community based subjects [31]. In another study patients who took acetaminophen were not more likely to have functional dyspepsia (OR 0.8 95% CI 0.5, 1.4) [32].

One of the strengths of this study was that the subjects are likely to truly represent people in the community who have upper GI symptoms. Subjects were identified by drawing a random sample of county residents rather than restricting the population to those presenting to a gastroenterologist or academic medical centre, reducing selection bias. Symptoms were verified by direct interview with a physician but endoscopy was not performed so some misclassification bias (e.g. missed peptic ulcer disease) cannot be excluded, although we would expect this to occur in only a small minority of cases. Another potential weakness of this study was the relatively low questionnaire response rate but there was no evidence of response bias in the sample obtained.

In summary, we observed novel associations with dyspepsia including a positive family history, sleep disturbances and somatization. It is conceivable these links are in turn explained by common genes and/or environmental exposures, and more work is needed to unravel these associations. Such work could lead to the identification of new therapeutic targets.

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Figure 1.
Flow Chart

Table 1
Univariate and Multiple Variable Analyses of Risk Factors For Dyspepsia in the Community Survey

Variable	% with dyspepsia	Univariate analysis [†]		Multiple variable analysis	
		OR(95% CI)	p-value	OR(95% CI)	p-value
Gender					
Female (n=118)	25%				
Male (n=106)	18%	1.5 (0.7,2.9)	0.27	0.9 (0.3,3.0)	0.9
Age Group					
<= 50yrs (n=59)	14%	1.1 [§] (0.9,1.4)	0.35	1.1(0.7,1.7)	0.6
> 50yrs (n=165)	25%				
Body mass index					
Normal (n=60)	27%	1.0 [*] (0.9,1.0)	0.31	0.9 (0.8,1.0)	0.1
Overweight (n=89)	21%				
Class I Obesity(n=41)	15%				
Class II obesity (n=15)	27%				
Class III Obesity (n=6)	17%				
Family history of indigestion					
Yes (n=91)	37%	6.1(2.7,14.0)	<0.001	3.4 (1.0,11.5)	0.048
No (n=98)	10%				
Family history of abdominal pain/ache					
Yes (n=75)	45%	8.6(3.8,19.7)	<0.001	4.7 (1.5,14.9)	0.008
No (n=111)	9%				
Family history of GERD					
Yes (n=86)	36%	4.4 (2.1,9.3)	<0.001		
No (n=108)	12%				
Family history of bowel dysfunction					
Yes (n=51)	43%	4.0(1.9,8.6)	<0.001		

Variable	% with dyspepsia	Univariate analysis †		Multiple variable analysis	
		OR(95% CI)	p-value	OR(95% CI)	p-value
No (n=133)	15%				
Insomnia					
Wake up not feeling rested					
Yes (n=80)	31%	2.6(1.3,5.1)	0.006		
No (n=139)	16%				
Difficulty falling asleep					
Yes (n=40)	38%	2.7(1.2,5.7)	0.01	8.2(2.2,31.5)	0.002
No (n=178)	18%				
Worsening of sleep problems during worsening bowel symptoms					
Yes (n=14)	79%	15.5(4.1,61.0)	<0.001	15.9(2.0,124.9)	0.009
No (n=177)	20%				
Waking up frequently at night					
Yes (n=96)	28%	1.8(0.9,3.5)	0.08		
No (n=123)	16%				
Over the counter med/prescription to sleep					
Yes (n=22)	36%	1.9(0.7,5.0)	0.23		
No (n=196)	20%				
Race					
Caucasian (n=175)	23%	1.5(0.6,3.8)	0.36		
Not Caucasian (n=46)	15%				
Somatic Symptoms					
SSC score > median (n=110)	34%	5.2(2.4,11.5)	<0.001	5.6(1.5,20.7)	0.01
SSC score <= median (n=109)	9%				
Medication Use					
Aspirin (n=120)	18%	0.7(0.4,1.3)	0.25	0.2(0.1,0.7)	0.01
Antacids (n=57)	35%	3.0(1.5,6.3)	0.003		
H2 blocker (n=22)	45%	3.9(1.5,10.0)	0.004	14.8(3.1,70.9)	0.0007

Variable	% with dyspepsia	Univariate analysis [†]		Multiple variable analysis	
		OR(95% CI)	p-value	OR(95% CI)	p-value
PPIs (n=23)	61%	9.4(3.6,24.9)	<0.001	7.3(1.7,31.4)	0.008
Acetaminophen (n=73)	34%	2.7 (1.3,5.3)	0.005		
Calcium Channel Blocker (n=10)	40%	2.71(0.66,11.10)	0.17		
Marital status					
Married (n=177)	21%	0.8(0.4,1.9)	0.66		
Not married (n=47)	24%				
Alcohol use					
Yes (n=107)	22%	1.1(0.6,2.1)	0.84		
No (n=117)	21%				
Nicotine use					
Yes (n=17)	29%	1.7(0.6,5.3)	0.34		
No (n=207)	21%				

[†] Adjusted for gender, age and Body Mass Index (BMI)

[§] per 10 years of age

^{*} per unit of BMI

PPI: Proton Pump Inhibitor

Table 2

Nested case-control study analysis of risk factors for dyspepsia

	Univariate analysis[†]	
Variable	OR & 95% CI	p-value
Gender		
Female (n=48)	1.1 (0.4,2.6)	0.9
Male (n=44)	1.0 (ref)	
Age Group	0.9 [§] (0.6,1.3)	0.5
<= 50yrs (n=34)		
> 50yrs (n=58)		
BMI	1.0 [*] (1.0,1.1)	0.3
Normal (n=26)		
Overweight (n=29)		
Class 1 Obesity (n=19)		
Class II obesity (n=7)		
Class III Obesity (n=2)		
<i>H. pylori</i> – positive (n=16)	3.1 (0.9,11.1)	0.08 [†]
<i>H. pylori</i> – negative (n=75)	1.0 (ref)	
Total calories	1.0 (1.0,1.0)	0.86 [†]
Total Protein	1.0 (1.0,1.0)	0.76 [†]
Total Carbohydrates	1.0 (1.0,1.0)	0.41 [†]
Total Fat	1.0 (1.0,1.0)	0.72 [†]
% protein	1.0 (0.8,1.1)	0.60 [†]
% carbohydrates	1.0 (0.9,1.0)	0.29 [†]
% fat	1.0 (1.0,1.1)	0.41 [†]

[§] per 10 years of age^{*} per unit of BMI[†] Adjusted for age, gender and BMI

Table 3

Composition of average daily intake based on responses to the Food Frequency Questionnaire among Cases and Controls

	Cases [n=52]	Controls [n=40]
Calorie intake	Mean $\pm$ SD	Mean $\pm$ SD
Total calorie intake [kcal]	1610.9 $\pm$ 705.2	1558.8 $\pm$ 643.5
Total protein [g]	68.9 $\pm$ 31.0	67.6 $\pm$ 26.5
Total carbohydrate [g]	189.7 $\pm$ 71.2	192.4 $\pm$ 78.6
Total fat [g]	62.9 $\pm$ 37.3	57.2 $\pm$ 31.5
Percent of total calories from		
Protein [%]	17.3 $\pm$ 3.1	17.6 $\pm$ 3.2
Carbohydrate [%]	48.4 $\pm$ 6.5	50.3 $\pm$ 9.2
Fat [%]	33.6 $\pm$ 6.6	31.8 $\pm$ 8.4