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Liver inflammation is a Risk Factor for Prediabetes in At-Risk Latinos with and without Hepatitis C Infection

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Abstract

Background and Aims—Early recognition of prediabetes can lead to timely clinical interventions to prevent type 2 diabetes. Both Latino ethnicity and chronic hepatitis C (HCV) have been identified as diabetic risk factors. We aimed to investigate predictors of impaired fasting glucose (IFG), a common prediabetic state, among Latinos with and without HCV.

Methods—One hundred Latino adults with no history of diabetes or cirrhosis underwent clinical, laboratory, and metabolic evaluation, including oral glucose tolerance testing (OGTT) and insulin suppression testing to quantify directly measured insulin resistance (IR). Isolated IFG was defined as fasting glucose 100mg/dL and <140mg/dL at 2 hours with normal glucose tolerance during OGTT.

Results—Overall subject characteristics included median age 44 years, 64% male, 40% HCV-positive, and 32% with isolated IFG. Factors associated with isolated IFG included subject age (OR 2.42 per decade, 95%CI 1.40–3.90, $p=0.001$), HCV infection (OR 4.0, 95%CI 1.71–9.72, $p=0.002$), and alanine aminotransferase (ALT) (OR 2.35 per doubling, 95%CI 1.46–3.77, $p<0.0001$). Multipredictor logistic regression analysis identified ALT (OR 2.05 per doubling, $p=0.005$, 95% CI 1.24–3.40) and age (OR 2.20 per 10 years, $p=0.005$, 95%CI 1.27–3.80) as factors independently associated with IFG. While HCV was associated with 4-fold higher odds of IFG, this entire effect was mediated by ALT.

Conclusions—We found strong evidence that liver inflammation is a risk factor for prediabetes among Latinos with and without HCV. Among HCV-infected individuals, early antiviral therapy could mitigate the effect of inflammation and represent an important intervention to prevent diabetes in this at-risk population.

Keywords

HCV; impaired fasting glucose; insulin resistance; Hispanics; ALT

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Introduction

More than one-quarter of all Americans have impaired fasting glucose (IFG) which, along with undiagnosed type 2 diabetes, has important health consequences [1]. Given that prediabetes is a modifiable and potentially reversible condition, early recognition and intervention can prevent progression to overt diabetes and associated complications [2]. Prediabetes is defined by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and eventually progresses to overt type 2 diabetes mellitus for the majority of subjects [3]. Importantly, the different types of prediabetes reflect potentially distinct pathophysiologic mechanisms based on the site where insulin resistance (IR) occurs. Peripheral IR, that which occurs in muscle and adipose cells, appears to play a greater role in IGT, whereas IFG has been associated predominantly with hepatic IR [4, 5]. Liver inflammation, such as that induced by viral hepatitis, may in turn play a role in the impairment of glucose metabolism by its potential impact on hepatic IR.

HCV infection is the most common cause of chronic liver disease in United States and increases the risk of incident diabetes in predisposed individuals [6]. In fact, diabetes is now considered an extra-hepatic manifestation of HCV infection [7]. HCV-induced IR has been implicated as the underlying mechanism of impaired glucose metabolism [8], yet it is not known whether the development of IR is a direct viral effect or secondary to HCV-induced inflammatory response. Moreover, the main site of IR in the setting of HCV is debated as occurring predominantly in the liver or in peripheral tissue, predominantly muscle [9–12]. While traditional risk factors such as older age, obesity, and family history of diabetes also play a critical role in development of diabetes in HCV, it has been shown that elevated liver enzymes, reflecting presence of liver inflammation, can be associated with incident diabetes [13–15]. Although these studies have excluded individuals with chronic viral hepatitis, it is also possible that HCV-induced liver inflammation may be important to the risk of developing prediabetes and in particular IFG.

At present, the complex interplay between host and viral factors underlying the development of impaired glucose metabolism in HCV is still poorly understood, yet relevant, given that glucose abnormalities are known to accelerate fibrosis, lead to worse disease outcomes in HCV-infected individuals, and also decrease response to anti-HCV therapy [8, 16]. Moreover, we have previously shown that nearly 40% of patients with chronic HCV have prediabetes, and IFG alone or in combination with IGT accounts for 75% of such cases [10]. Higher grade of HCV-induced liver inflammation on liver biopsy was independently predictive of IFG in this study [10]. Thus, the identification of potentially modifiable factors associated with IFG may be relevant to management of HCV-infected individuals.

Latinos, the largest ethnic minority group in the US, are disproportionately affected by HCV infection, and the course of HCV-induced liver disease is more aggressive than for other ethnic groups [17]. In epidemiologic studies, Latinos also have exceptionally high rates of prediabetes [18] and therefore, Latinos with HCV infection represent an exceptionally high risk population. While the exact prevalence of prediabetes in HCV-infected individuals is not clearly known, it appears higher than for both uninfected controls and those with non-

HCV chronic liver disease, according to limited reports [19, 20]. In this study, we aimed to evaluate factors associated with isolated IFG, including HCV infection, using a prospective cohort of non-diabetic Latinos and comprehensive clinical, virologic, and metabolic measures. We hypothesized that severity of liver inflammation, rather than a direct viral effect, is associated with the presence of IFG in HCV-infected individuals.

Research Design and Methods

Patient Selection

Latino adults with or without chronic HCV infection were recruited from San Francisco General Hospital and affiliated clinics at the University of California San Francisco between 2008 and 2013. Participants had no history of type 2 diabetes or liver cirrhosis. HCV infection was confirmed by serologic evidence of anti-HCV antibody and detectable plasma HCV viral load by PCR. Inclusion criteria were Latino ethnicity (as determined by self-report of the participants and both biological parents and four biological grandparents) [21], BMI ≥ 20 kg/m², willingness to consent, and ability to participate in testing. HCV-uninfected individuals were included if they had no known history of liver disease, and screened negative for HCV, HBV, and HIV infection. Individuals were excluded if they had previously undiagnosed diabetes (fasting plasma glucose, FPG ≥ 126 mg/dL on OGTT), a history of diabetes, or use of anti-diabetic agents. Further exclusion criteria in HCV-infected individuals included liver disease other than HCV, HIV co-infection, clinical evidence or known history of cirrhosis or decompensated liver disease, and prior or current HCV therapy. Prior to enrollment this study was approved by the UCSF Committee on Human Research.

Metabolic Evaluation

All participants underwent a comprehensive medical interview, physical examination including anthropometric measures, and fasting laboratory evaluation which required a 2-day hospital admission at the UCSF Clinical and Translational Science Institute – Clinical Research Center for study procedures. On day one, a 75-g oral glucose tolerance test (OGTT) was performed after an overnight 12-h fast. Based on OGTT results, participants who met diagnostic criteria for diabetes or impaired glucose tolerance (IGT), defined as 2-hour plasma glucose ≥ 140 mg/dL, were excluded from further analysis. Participants were then classified as having either normal or isolated impaired fasting glucose (IFG), defined as FPG ≥ 100 and <126 mg/dL [22]. On day two, following another overnight 12-hour fast, participants underwent modified 240-min insulin suppression test (IST) as previously described [23]. During this test, new glucose production is inhibited, and similar plasma levels of exogenous insulin are reached in all individuals. The steady-state plasma glucose (SSPG) concentration resulting from an identical glucose infusion rate in all subjects is a direct measure of insulin-mediated glucose uptake in muscle. Higher SSPG levels represent higher degrees of peripheral IR which was operationally defined as SSPG >180 mg/dL, a value that has been shown to significantly increase the risk of developing clinical syndromes associated with IR in prospective studies [24].

Statistical Methods

Characteristics of study participants were summarized using mean $\pm$ SD, median or interquartile range, and frequency. Continuous variables were centered and scaled as appropriate to allow for meaningful interpretation of regression coefficients. All predictor variables were assessed for linearity and normality and adjusted as necessary; ALT was transformed to log base-2 to estimate the effect per doubling of ALT level. Bivariate logistic regression was used to model the relationship between the binary outcome IFG and selected predictor variables. Multivariable stepwise forward selection logistic regression modeling was used to evaluate the host and viral correlates associated with IFG from an *a priori* compiled list. Statistical significance was assessed at a p-value of <0.05 (2-sided) in all models. All analyses were performed using Stata version 12 statistical software, Stata Corp LP, College Station, TX.

Results

Baseline Characteristics

A total of 100 study participants who met the inclusion/exclusion criteria were analyzed (Table 1). The overall cohort characteristics were significant for median age 44 years, 64% male, 40% HCV-positive, and 35% born in the US. Overall, 32 subjects had isolated IFG and 68 had normal fasting glucose (NFG). The mean SSPG was 146 mg/dL, and overall 26% of the total were insulin resistant (SSPG >180 mg/dL). A total of ten participants (10%) met criteria for metabolic syndrome based on presence of three or more clinical criteria including increased waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting glucose [25].

Among HCV-infected participants, the median ALT was 84.6 ± 53.0 U/L, mean $\log_{10}$ HCV viral load 5.8 ± 0.6 IU/mL, 67% were HCV genotype 1 (19% genotype 2, 14% genotype 3). Thirty four (85%) of HCV-infected patients underwent liver biopsy, with 67.6% having grade 2 inflammation, 44.1% having stage 2 fibrosis, and 26.5% with steatosis without evidence of steatohepatitis, using the Ludwig-Batts scoring system. Although liver biopsy is often clinically indicated and standard of care for HCV-infected patients, healthy controls were not subjected to invasive liver biopsy for this study.

Characteristics of participants with and without isolated IFG were similar except subjects with IFG were older, more likely to be US-born, have HCV infection (63 vs 29%), have higher mean SSPG and be insulin resistant (34 vs 22%), and have higher ferritin levels. In addition, a lower proportion of participants with IFG consumed a moderate amount of alcohol. Overall, ALT levels were significantly higher (mean ALT 72 vs 39 U/L) for those with isolated IFG versus NFG (Figure 1A). Although all participants had higher mean ALT levels in the setting of IFG vs NFG, when stratified by HCV status (95 vs 75 for HCV-infected and 35 vs 24 U/L for controls), statistical significance was reached in the HCV-uninfected group ($p=0.002$) (Figure 1B).

Factors associated with IFG

On single-predictor analysis (Table 2), subject age (OR 2.42 per decade, 95%CI 1.40–3.90, $p=0.001$), HCV infection (OR 4.00, 95%CI 1.71–9.72, $p=0.002$), ALT level (OR 2.35 per doubling, 95% CI 1.46–3.77, $p<0.0001$), and ferritin level (1.05, 95%CI 1.03–1.12, $p=0.027$) were positively associated with isolated IFG. In addition, metabolic syndrome (OR 2.33) and US birth were positively associated (OR 2.10), while moderate alcohol consumption was negatively associated (OR 0.39) with IFG, but these did not quite reach statistical significance. We further assessed whether the association of HCV with isolated IFG was mediated through liver inflammation as hypothesized using logistic modeling with and without ALT. The statistically significant four-fold higher odds of IFG for HCV-infected subjects disappeared. Sobel-Goodman mediation testing was then used to assess the statistical significance of this mediation effect and the proportion of the total effect of HCV status on IFG was explained by ALT levels. After adjusting for age, the estimated proportion of the effect explained was 1.43 (i.e. more than all of this effect and the adjusted effect was reversed), but the uncertainty around this was large (95% CI -0.70 – 12.49). This reflects uncertainty about the direct effect of HCV (not mediated by ALT), which cannot be accurately estimated due to the strong association of HCV with ALT.

In multivariable analysis using stepwise forward selection logistic regression (Table 2), participant age (OR 2.20 per 10 year increase, 95%CI 1.27–3.80, $p=0.005$) and ALT levels (OR 2.05 per doubling of ALT, 95%CI 1.24–3.40, $p=0.005$) were the only statistically significant independent predictors of isolated IFG. When additional variables were added to the primary multi-predictor model, which controlled for BMI and sex, the OR for age and ALT were not substantially altered. Metabolic syndrome was associated with an OR for IFG of 4.7 when added to the primary model and this approached statistical significance (95%CI 0.93–23.70, $p=0.062$). US birth was associated with an OR of 1.7 although this did not reach significance ($p=0.30$). Finally, when HCV was included, the OR for both age and ALT were augmented (2.30 and 2.34 respectively) and remained significant, while HCV had no significant independent association with IFG (OR=0.70, 95%CI 0.17 to 2.9, $p=0.62$).

Discussion

This is the first study to evaluate factors associated with isolated IFG among non-diabetic Latinos, inclusive of HCV infection, utilizing comprehensive metabolic testing including directly measured insulin resistance. In the subjects studied, IFG was highly prevalent, affecting one-third of subjects. Age and degree of liver inflammation, as reflected by ALT levels, were highly predictive of IFG. While a higher proportion of HCV-infected subjects had IFG, the association between HCV and IFG appeared to be mediated by severity of liver inflammation.

Impaired fasting glucose, a precursor to diabetes, affects approximately 26% of the US population, with considerable variability by age, gender, and ethnicity [5]. Latinos are the largest and fastest growing ethnic minority in the US and are disproportionately affected by impaired glucose metabolism [26]. Further, Latinos appear to progress from prediabetic states to overt clinical diabetes faster than non-Hispanic whites and have a higher risk of prediabetes independent of traditional risk factors, including obesity [18]. The prevalence of

IFG across all Latinos is not clearly known, as this ethnic group encompasses a diverse and highly admixed population [27]. With regard to prediabetes, Mexican Americans are the most well studied Latino population and the overall prevalence of isolated IFG according to NHANES data is 30% (42.2% for men and 21.2% for women) [5, 28]. Similarly, we found that 32% of our Latino cohort had isolated IFG, 26% of whom were Mexican American. It is known that both US birth and a longer duration of US residence impacts the risk of obesity and diabetes [29]. Similarly we observed two-fold higher odds of IFG in Latinos that were born in the US, although this was no longer statistically significant when ALT and age were controlled for. It is likely that dietary and lifestyle factors play a significant role in the development of diabetes among foreign born at-risk populations through acculturation over time [30].

Increasing age is a well-established risk factor for prediabetes [1] and similarly in this study, the odds of IFG rose by more than two-fold per decade. Prediabetes is less prevalent among females based on epidemiologic studies [31], and similarly female sex was associated with lower odds (OR=0.74) of IFG in this study, though this did not reach statistical significance. In addition, while obesity is closely linked to a spectrum of metabolic conditions including prediabetes, Latinos, in particular, have higher risk of prediabetes at a lower body weight [18] and hence, obesity does not fully account for increased diabetic risk in this population. Anthropometric measures of obesity were positively associated with IFG in this study. Indeed, the upper limit of the confidence interval for BMI was a nearly 2-fold increase in odds of IFG per 5 point increase in BMI, so our results were compatible with a substantial effect of obesity. The high prevalence of obesity in this Latino cohort (mean BMI 27), that is representative of the Latinos in US, may have precluded higher odd ratio estimates that may be observed in patient cohorts with a wider range of BMI distribution. Since IFG is predominantly characterized by hepatic insulin resistance, similar to prior studies IFG was not independently associated with peripheral insulin resistance, though the direction of association was positive [10].

In addition to traditional diabetic risk factors, several studies have shown a link between elevated liver enzymes (ALT and GGT), reflective of hepatic inflammation, and the development of overt diabetes in different ethnic groups [11, 13, 32, 33]. Less is known about the association of hepatic inflammation with prediabetes and few studies have shown an association between IFG and elevated liver enzymes [15, 34]. In this present study, the odds of IFG were two-fold higher for each doubling of ALT. Similarly, in a study of non-diabetic Pima Indians, another high risk ethnic minority group, elevated ALT was specifically and independently associated with a decline in hepatic insulin sensitivity and elevated hepatic glucose output, hence fasting hyperglycemia [13]. Several mechanisms have been proposed to explain this correlation between liver enzymes and isolated IFG. In general, ALT reflects an ongoing inflammatory process in the liver with development of oxidative stress and release of pro-inflammatory cytokines, particularly TNF- α and IL-6 that lead to inhibition of key elements of the insulin signaling pathway [35]. This then leads to hepatocyte resistance to the effects of insulin and lack of normal suppression of hepatic glucose production and glycogenolysis, thereby resulting in fasting hyperglycemia or IFG [36].

Chronic HCV infection, which results in liver inflammation, has been specifically associated with diabetes and IR [37]. In turn, diabetes and IR impact the course of HCV and portend a more rapid progression of liver fibrosis [8]. In a prior study of HCV-infected patients, we showed that higher grade of liver inflammation on biopsy was independently predictive of IFG [10]. In this current study, we further explored the relationship between HCV-induced inflammation and IFG by comparing HCV-infected with uninfected controls, and found that presence of HCV was associated with four-fold increased odds of IFG. Our analysis concluded that the entire effect of HCV on IFG was mediated through liver inflammation, while evidence against any direct viral effect was weak. These findings are in accordance with a recent prospective cohort study by Montenegro et al that documented an association between HCV and incident diabetes only if HCV infection was also associated with ALT elevation [14]. Further, in an analysis of NHANES data, Ruhl et al [38] found that elevated ALT was associated with increased odds of diabetes regardless of HCV status, suggesting that nonspecific liver inflammation, rather than a direct HCV viral effect, underlies diabetic risk. The authors hypothesized that the association of HCV and diabetes found in prior clinical series may be related to over-representation of patients with advanced HCV, likely to have higher degrees of liver enzyme activity. At any rate, HCV-induced liver inflammation appears to be an important modifiable risk factor for prediabetes, and reduction of liver inflammation through viral eradication with increasingly effective direct acting HCV antivirals may be relevant to diabetes prevention.

The limitations of this study include sample size, which was restricted by the logistics of performing extensive 2-day metabolic testing including directly measured IR, which would be impractical with a larger cohort. Nevertheless, the number of participants enrolled in this study represents the largest Latino population with and without HCV infection assembled using such measures to date. Further, inclusion of a group of HCV uninfected subjects for comparison represents an important strength. Long term prospective follow-up of the study participants would be required to evaluate a cause and effect relationship between severity of HCV-induced liver inflammation and development of IFG which could not be established in this study.

This study is unique in evaluating predictors of prediabetes in an at-risk cohort of Latinos, a growing population disproportionately affected by overlapping epidemics of HCV and metabolic disease. It has been proposed that appropriate screening and management of IFG may be particularly relevant in the setting of HCV. We found strong evidence that liver inflammation is also a potentially modifiable risk factor for IFG. Therefore, early viral eradication and thus reduction of liver inflammation with anti-HCV therapy is important for diabetes prevention among Latinos, especially older individuals at highest risk for impaired glucose metabolism and its clinical consequences.

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List of Abbreviations

HCV	Hepatitis C virus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
OGTT	Oral glucose tolerance testing
IR	Insulin resistance
ALT	Alanine aminotransferase
BMI	Body mass index
HBV	Hepatitis B infection
HIV	Human immunodeficiency virus
FPG	Fasting plasma glucose
NFG	Normal fasting glucose
SSPG	Steady-state plasma glucose
HDL	High density lipoprotein
GGT	Gamma glutamyltransferase

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Key Points

- This is the first study to evaluate the impact of HCV infection as a risk factor for prediabetes among non-diabetic Latinos at risk for metabolic disease.
- This study utilizes comprehensive metabolic testing including directly measured insulin resistance.
- In this study, age and degree of liver inflammation were highly predictive of isolated impaired fasting glucose (IFG).
- Importantly, the association between HCV and IFG appeared to be mediated by severity of liver inflammation.

A.

§ $P < 0.001$ for the difference in mean ALT between subjects with NFG and IFG.

B.

‡ $P < 0.01$ for the difference in mean ALT between subjects with NFG and IFG in HCV negative subjects.

Figure 1. Box plots of differences in alanine aminotransferase (ALT) levels

Figure 1A. ALT levels categorized by normal (NFG) and impaired fasting glucose (IFG).

Figure 1B. ALT levels in subjects with and without HCV infection categorized by normal (NFG) and impaired fasting glucose (IFG).

Table 1

Characteristics of Subjects with (IFG) and without (NFG) Isolated Impaired Fasting Glucose

Characteristic	All Subjects N=100	IFG N = 32	NFG N = 68	p-value
Mean age (years) Median, interquartile range	42 ± 10 44 (33–50)	47 ± 8 48 (42–53)	39 ± 10 40 (30–48)	0.0006
Male sex (%)	64	72	60	0.26
US born (%)	35	47	29	0.090
HCV infection (%)	40	63	29	0.0017
Metabolic Syndrome (%) [*]	10	5	5	0.32
Insulin resistant (%)	26	34	22	0.19
Mean SSPG (mg/dL)	136 ± 74	158 ± 77	126 ± 70	0.029
Mean BMI (kg/m ²)	27 ± 5	27 ± 4	27 ± 5	0.30
Mean waist circumference (cm)	93 ± 11	94 ± 10	92 ± 12	0.27
Alcohol consumption [§] Moderate Heavy	36 24	8 7	28 17	0.064 0.29
Current smoker (%)	25	22	26	0.62
Diabetes family history (%)	65	66	65	0.93
Elevated blood pressure (%) ^{**}	11	10	13	0.74
Median fasting glucose (range) (mg/dL)	95 (76–116)	92 (76–99)	102 (100–116)	<0.0001
Mean ALT (U/L)	50 ± 45	72 ± 60	39 ± 31	<0.0001
Mean AST (U/L)	40 ± 28	54 ± 40	34 ± 18	0.063
Mean ferritin (ng/mL)	103 ± 97	136 ± 104	87 ± 90	0.0024
Mean LDL (mg/dL)	106 ± 28	105 ± 28	106 ± 29	0.75
Mean HDL (mg/dL)	54 ± 14	56 ± 15	53 ± 14	0.50
Mean TG (mg/dL)	116 ± 65	98 ± 48	109 ± 72	0.68

^{*} Diagnosis of metabolic syndrome was based on presence of 3 clinical criteria including increased waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting glucose [25]

^{**} High blood pressure was defined as use of anti-hypertensive therapy or systolic ≥ 130 and/or diastolic ≥ 85 mmHg [25].

[§] Subjects were categorized according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as moderate (3 drinks per day and 7 drinks per week for women, 4 drinks per day and 14 drinks per week for men) or heavy drinkers [39].

Table 2

Single-predictor and multivariate evaluation of potential risk factors for impaired fasting glucose (IFG)

Predictors	One-predictor Models			Multi-Predictor Models*		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (per decade)	2.42	1.40–3.90	0.001	2.20	1.27–3.80	0.005
Log ₂ ALT (U/L)	2.35	1.46–3.77	<0.0001	2.05	1.24–3.40	0.005
Female sex	0.60	0.20–1.52	0.26	0.74	0.26–2.07	0.56
BMI (per 5 kg/m ²)	1.20	0.80–1.82	0.48	1.19	0.72–1.96	0.51
HCV infection	4.00	1.71–9.72	0.002	0.70	0.17–2.90	0.62
Insulin resistance	1.85	0.73–4.72	0.19	1.40	0.43–4.52	0.56
Metabolic Syndrome	2.33	0.62–8.73	0.21	4.68	0.93–23.70	0.062
Alcohol consumption	0.39	0.14–1.05	0.061	0.49	0.16–1.51	0.21
Moderate	0.83	0.54–1.67	0.24	0.52	0.15–1.84	0.31
Heavy						
Current tobacco smoking	0.80	0.34–2.12	0.62	0.31	0.09–1.02	0.055
Diabetes family history	1.04	0.42–2.53	0.93	1.11	0.38–3.24	0.85
US born	2.10	0.91–5.00	0.092	1.69	0.63–4.50	0.29
Ferritin (per 10 ng/mL)	1.05	1.03–1.12	0.034	1.03	0.97–1.09	0.33
LDL (per 10 mg/dL)	1.03	0.85–1.17	0.83	1.02	0.86–1.22	0.78
HDL (per 5 mg/dL)	1.05	0.91–1.20	0.46	1.16	0.93–1.34	0.24
Triglycerides (per 10 mg/dL)	0.99	0.93–1.02	0.43	0.99	0.89–1.06	0.50

* The first four predictors were included in the primary multi-predictor model. Remaining results, shown in *italics*, are the results for each remaining predictor when added to that primary model in 5-predictor models.