Polypharmacy and Frailty Among Persons With HIV

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Abstract

Polypharmacy is associated with frailty in the general population, but little is known about polypharmacy among virally suppressed persons living with HIV (PLWH) who receive antiretroviral (ARV) therapy. We aimed to determine the association between polypharmacy and an adapted frailty-related phenotype (aFRP) in PLWH and uninfected veterans by conducting a cross-sectional study from October 2008 - September 2009 of 1762 PLWH on ARV with suppressed HIV viral load and 2679 uninfected participants in the Veterans Aging Cohort Study who completed a survey. The primary predictor was number of chronic outpatient non-ARV medications (received for 90 consecutive days allowing for a 30-day gap between refills) using electronic pharmacy fill/refill data. The outcome was self-reported endorsement of any of the four aFRP domains: shrinking, exhaustion, slowness, or low physical activity. Based on prior established methods, frailty was defined as reporting 3–4 domains while pre-frailty was 1–2 domains. Frailty was uncommon (2% of PLWH, 3% of uninfected); a larger proportion demonstrated any aFRP domain (31% PLWH, 41% uninfected). Among PLWH and uninfected participants, the median number of chronic non-ARV medications was 6 and 16 respectively for those with any aFRP domain and 4 and 10 for those without aFRP domains. In adjusted analyses, each additional chronic non-ARV medication conferred an 11% increased odds of having any aFRP domain in PLWH and a 4% increased odds in those who were uninfected (odds ratio (OR) [95% CI] = 1.11 [1.08, 1.14]); uninfected (OR [95% CI] = 1.04 [1.03, 1.04])]. The interaction between HIV and medication count was significant, p<0.001. While domains of aFRP were commonly reported, few had more than one. Chronic non-ARV medication count was strongly

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associated with endorsing aFRP domains. The stronger association between polypharmacy and frailty in PLWH warrants further study and potential deprescribing of medications.

INTRODUCTION

Effective antiretroviral (ARV) treatment has dramatically extended the life expectancy for persons living with HIV (PLWH) and committed them to lifelong treatment with at least three medications ((OARAC), 2018). PLWH have higher rates of many diseases associated with aging than uninfected individuals and guidelines recommend equally aggressive treatment for these conditions (Abrass, 2012). Therefore, polypharmacy (use of 5 or more concurrent medications) is now common among those aging with HIV (Edelman et al., 2013; Ware et al., 2018). While polypharmacy is closely associated with frailty in the general population (Gnjidic et al., 2012), ARV treatment is clearly life-preserving and little is known about the implications of non-ARV polypharmacy among PLWH. One study did find that non-ARV polypharmacy was associated with an increased risk of falls in PLWH who had substance dependence, while another found a higher prevalence of frailty in PLWH from Uganda who had polypharmacy(Kim et al., 2018; Ssonko et al., 2018).

Frailty is an increased vulnerability to and reduced ability to recover from stressors due to a depletion of physiologic reserve (Bortz, 2002). Different approaches to measure frailty are still being explored. Rockwood describes a physiologically-based approach to frailty: a cumulative deficit model that is a sum of symptoms, signs, laboratory abnormalities, diseases, and disabilities (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; K. Rockwood, 2005; Kenneth Rockwood & Mitnitski, 2011). The more deficits a patient accumulates, the higher risk he or she has for adverse outcomes. Another approach by Fried that was validated in the Cardiovascular Health Study(Fried et al., 2001) is based on a clinical syndrome, where frailty is based on the presence of at least 3 of 5 phenotypic domains: physical shrinking, exhaustion, slowness, low physical activity, and weakness (Fried et al., 2001; Walston et al., 2006). Önen developed a version of the Fried frailty phenotype that modified the definitions of unintentional weight loss and low physical activity (Onen et al., 2009). Unintentional weight loss included Fried's definition of a greater than 10 pound weight loss in the past year, but also added an alternative definition of losing greater than 5% of the previous year's body weight (Onen et al., 2009). Low physical activity was determined by having participants self-report their ability to participate in vigorous activities, different from Fried's defining it by the number of kilocalories burned per week (Onen et al., 2009).

Utilizing the Önen frailty phenotype, researchers found that HIV infection was independently associated with prefrailty and frailty in PLWH 45 years compared to participants without HIV. The Multicenter AIDS Cohort Study (MACS) amended the Fried frailty approach for HIV-infected participants using survey data (Akgun et al., 2014). This

measure is called the frailty related phenotype (FRP) because it captured the first four domains of the Fried frailty phenotype, as the pre-existing survey did not include questions measuring weakness (Akgun et al., 2014). Using the FRP, frailty was defined as present for participants who endorsed at least 3 domains and pre-frailty for 1 to 2 domains (Akgun et al., 2014). Using similar survey items and frailty domains as utilized by the MACS, researchers showed that an adapted frailty-related phenotype (aFRP) was associated with hospitalization and mortality in PLWH and uninfected participants in the Veterans Aging Cohort Study (VACS) (Akgun et al., 2014). The VACS Index 2.0 includes objective lab measurements to predict mortality and has also found to be predictive of frailty outcomes, a potentially useful tool to assess physiologic frailty in patients to indicate whether they need a comprehensive geriatric assessment. Furthermore, the association of polypharmacy with the VACS Index has been previously reported (Amy C. Justice et al., 2018). As frailty is associated with adverse outcomes, it is important to understand the role of potentially modifiable factors that contribute to aFRP.

Thus, the aim of our current study is to assess the association between polypharmacy, as measured by chronic non-ARV medication count, and frailty, based on the aFRP, among PLWH and uninfected VACS participants. Understanding whether and how polypharmacy is associated with frailty among PLWH and uninfected participants can better inform clinical decision-making towards deprescribing potentially inappropriate medications (PIMs) for individuals aging with HIV.

METHODS

Sample

We used data from the VACS, a multi-site prospective study of PLWH participants and age, race/ethnicity, and site-matched uninfected participants receiving care through the Veterans Health Administration system (VA). The VACS includes VA electronic medical record and survey data. We conducted a cross-sectional analysis of 1762 PLWH receiving ARV and 2679 uninfected veterans for Fiscal Year (FY) 2009 (October 2008 through September 2009). PLWH participants were considered to be receiving ARV therapy if they received at least three antiretroviral agents, excluding low dose ritonavir used to boost levels of other protease inhibitors (Gandhi et al., 2013).

Inclusion criteria were participants receiving any non-antiretroviral (non-ARV) prescriptions twelve months prior to FY2009, to ensure participants were receiving their medications through the VA. Their last follow-up date had to occur after FY2009 to ensure they were continuing to receive care and had not died. To study participants adherent to long-term ARV, we restricted to those with suppressed HIV-1 RNA, defined as   400 copies/mL within 6 months of the start of FY2009. We excluded participants with a cancer diagnosis (except for non-melanoma skin cancer). Uninfected participants who had a recorded CD4 count or an unsuppressed HIV-1 RNA or ARV receipt were likely either misclassified or new seroconverts, and were excluded for having an ambiguous HIV status. The VACS cohort was approved by the institutional review boards of the VA and the Yale University School of Medicine. Informed consent was obtained from all participants, who were reimbursed $20 for their participation.

Primary predictor

The primary predictor variable, chronic non-ARV medication count, was determined using VA electronic pharmacy fill/refill data. Medications were considered chronic when prescribed for at least 90 consecutive days, allowing gaps up to 30 days between refills. We determined receipt of all outpatient preparations (i.e. oral, inhaled, injectable, etc.) of medications dispensed through the VA using data available through the Pharmacy Benefits Management program (Fultz et al., 2006). Prescriptions that were excluded were diagnostic supplies (i.e. glucose test strips), emollients, eyewashes, lubricants, soaps, shampoos, soap-free cleaners, mouthwashes, sun protectants and screens, irrigation solutions, ceruminolytics, deodorants, antiperspirants, and contact lens solutions. Medications were categorized according to VA class (Development, February 2006 (revised)). We determined the median number of chronic non-ARV medications received for each participant during the one-year time period in FY2009. Individual medications that were included in co-formulated products were counted separately.

Outcome

The outcome variable was endorsement of any aFRP domain based on participants' answers to a survey completed at VACS enrollment. The domains were physical shrinking, exhaustion, slowness, and low physical activity (Textbox). If the participant had 3 domains they were classified as frail, and if they endorsed 1 to 2 domains they were classified as pre-frail. Participants without any of the elements were classified as not frail. Even though the survey was created prior to the study of the FRP in MACS, VACS aFRP survey items closely matched those of the MACS, except for the item used to define exhaustion. Because frailty was uncommon (3% of the participants) using these definitions, we broadened the definition of the study outcome to endorsing "any aFRP domain". Participants had any aFRP domain if they reported having one or more domain.

Covariates:

We included socio-demographic variables (gender, race/ethnicity) based on self-report through survey. Comorbidities were included using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) diagnosis codes or clinical data when available (see Supplementary Table 1). A comorbid condition was identified based on at least one inpatient or two outpatient ICD-9 codes for the condition, modeled off of previously described methods(Goulet et al., 2007). We also determined hospitalization using VA inpatient files and mortality using the VA Vital Status File captured from the end of FY09 (September 30, 2009 through June 30, 2014).

Analyses

Descriptive analyses were performed comparing PLWH to uninfected participants stratified by endorsing any aFRP domain. We evaluated significant differences using the Chi-square test for the categorical variables, t-test for normally distributed, and Wilcoxon-signed rank test for non-normally distributed continuous variables. Multivariable regression models were created to determine associations between chronic non-ARV medication count and having any aFRP domain versus being not frail. We also determined associations between chronic

non-ARV medication count and each of the aFRP domains. Unadjusted and adjusted odds ratios were calculated, stratified by HIV status. Variables that were statistically significant in bivariate analyses and that were not collinear based on Pearson correlation and the Variance Inflation Factor or were clinically relevant were evaluated. Those that remained significant after adjustment were retained in the final parsimonious model. Statistical significance was defined as p<0.05. The interaction between non-ARV medication count and HIV status was calculated. All statistical tests were performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Participant Characteristics

Our analytic sample (1762 PLWH, 2679 uninfected) was predominantly male (94%), racially/ethnically diverse (64% black, 10% Hispanic), and 96% had at least one comorbid condition (Table 1). 37% of the sample reported at least one aFRP domain (31% of PLWH, 41% of uninfected). Among those with any frailty domain, when compared to uninfected, PLWH participants were more likely to have Hepatitis C (55% vs. 31%) liver disease (56% vs. 32%), liver fibrosis with a fibrosis FIB-4 score of >3.25 (9% vs. 2%), to be hospitalized (25% vs. 20%), and to have died (16 vs. 4%). Very few patients had 3 or more domains of the aFRP (2% PLWH, 3% uninfected).

Chronic Non-Antiretroviral Medication Counts

The median chronic non-ARV medication counts for the PLWH and uninfected participants were 4 and 12 respectively (p<0.001). This difference remained significant when we stratified by aFRP domains (Table 2). Overall, the three most common chronic non-ARV medications were antilipemics, angiotensin-converting enzyme (ACE) inhibitors and antidepressants, which varied by HIV status and having any aFRP domain (Table 2).

Factors associated with aFRP

In unadjusted logistic regression analyses, each additional chronic non-ARV medication was associated with having any aFRP domain, [(OR) [95% CI]] = 1.05 [1.04, 1.05]). In the adjusted model (Table 3), each additional chronic non-ARV medication conferred a 4% increased odds of having an aFRP domain (OR [95% CI] = 1.04 [1.03, 1.05]) in the sample overall. Other predictors of domains of aFRP were Hepatitis C and chronic pain-related diagnoses. HIV infection was not significant. Black race and male gender had an inverse association with having any aFRP domain.

Chronic non-ARV medication count was the single best predictor (chi-square, χ^2=142), and chronic pain-related diagnoses the second strongest predictor (χ^2=46) for having aFRP domains. There was a significant interaction between median chronic non-ARV medication count and HIV infection of p<0.001. In models stratified by HIV status, chronic non-ARV medication count conferred an 11% increased odds of having an aFRP domain among PLWH and 4% among uninfected, (OR [95% CI] = 1.11 [1.08, 1.14]) and (OR [95% CI] = 1.04 [1.03, 1.04]), respectively (Table 4). Hepatitis C infection and chronic pain remained significant for increased odds of having aFRP domains in the stratified models

adjusted for key covariates for both groups. Adding CD4 count to the adjusted model did not significantly change our findings and CD4 count had a low associated chi-square of 0.01.

DISCUSSION

In this sample of PLWH and uninfected VACS participants, over a third of participants had at least one aFRP domain but few had three or more aFRP domains. PLWH, regardless of having aFRP domains, were on fewer chronic non-ARV medications than their uninfected counterparts. Chronic non-ARV medication count was the single best predictor of having aFRP domains among both PLWH and uninfected participants, with a stronger association seen in PLWH.

In our study, frailty was uncommon, similar to findings in the MACS (Desquilbet et al., 2009). However in contrast to the MACS, our PLWH participants were on fewer non-ARV medications than those uninfected in our study (Ware et al., 2018). This may because the uninfected participants from the MACS were from the community, while those from the VACS were clinic patients. Therefore, the MACS uninfected participants were likely less ill and therefore on fewer chronic non-ARV medications

There are reasons to think that polypharmacy contributes to frailty. One prospective study found that for older people who are prescribed 10 or more drugs, there was a decline in cognitive function, a condition seen in older patients with frailty(Jyrkka, Enlund, Lavikainen, Sulkava, & Hartikainen, 2011). Another study found that polypharmacy was associated with incident frailty in older community-dwelling men [AOR ([95% CI] = 2.45[1.42, 4.23])] (Gnjidic et al., 2012). And even when adjusting for comorbidities to account for frailer participants having more comorbidities and therefore may have been prescribed more medications, the association persisted. They suggested two possible reasons for this: one, participants who were taking more medications had more severe disease or two, polypharmacy may contribute to frailty (Gnjidic et al., 2012). It is likely that the relationship is cyclical: polypharmacy leads to a frailty related event (i.e. a fall), which leads to more polypharmacy (i.e. pain medications), which may then lead to more frailty events. Our study demonstrating that chronic pain related conditions was the second strongest predictor of frailty is supportive of this hypothesis. Other studies have also found increasing prevalence of opioid prescribing in aging PLWH and uninfected participants and that opioid prescription contributes to fractures, a frailty related outcome (Becker et al., 2016, 2017; Saunders et al., 2010). Furthermore another study of PLWH with substance dependence found that polypharmacy was associated with falls, another frailty related outcome (Kim et al., 2018).

Despite lower prevalence of frailty among PLWH in our study, their risk of frailty associated with polypharmacy was greater. Lower absolute risk of frailty in our study for those with HIV is likely due to our restricting the sample to those on ARVs with suppressed HIV-1 RNA. In prior work we found that PLWH participants with suppressed HIV-1 RNA had lower prevalence of frailty (measured by aFRP) than those with detectable HIV-1 RNA (Akgun et al., 2014). Nevertheless, in PWLH participants, each additional non-ARV medication conferred an 11% increased odds of having aFRP domains and a 4% increased

odds in those who were uninfected. This association in PLWH participants is likely due to the fact that those living with HIV are more susceptible to the harms of polypharmacy because of decreased organ system reserve, chronic inflammation, and ongoing immune dysfunction (Deeks & Phillips, 2009; Edelman et al., 2013; A. C. Justice, 2010). They also have an increased prevalence of liver and renal disease, which can cause harmful changes in drug metabolism as well as cause potential drug-drug interactions with ARVs (Joshi, O'Grady, Dieterich, Gazzard, & Agarwal, 2011; Lucas et al., 2007).

The 10 most common chronic non-ARV medication classes among PLWH and uninfected in our study were similar to results found in observational studies of polypharmacy among older adults (Gnjidic et al., 2012; Maher, Hanlon, & Hajjar, 2014). Lower chronic non-ARV medication counts among PLWH compared with uninfected veterans may be explained by the reluctance of physicians to add medications to the regimen of PLWH (Burkholder et al., 2012; Freiberg et al., 2009). However, when non-chronic and ARV medications were included for a total medication count, the virally suppressed PLWH participants had higher medication counts compared to those uninfected.

There are a few limitations to this study. First, using VA electronic medical records as our measure for medication count likely underestimates medication count by omitting medications from outside pharmacies, over-the-counter, vitamins, other supplements, and those from inpatient hospitalizations. However, we likely have an accurate measure of the number of medications from the VA that participants were consuming as we defined medication count utilizing pharmacy fill/refill data rather than prescription data. Second, the sample studied was predominantly male and of relatively younger age (mean age 56) compared to the geriatric population in which the frailty phenotype has been more completely characterized (typically >65 years old) (Clegg et al., 2013; Fried et al., 2001). Third, the VACS aFRP, similar to the MACS FRP does not account for weakness, which is included in the phenotype developed by Fried (Akgun et al., 2014).

In the general medical population, frailty has strong associations with adverse outcomes including geriatric syndromes (i.e. falls, fragility fractures, and cognitive decline), hospitalizations, and mortality (Walston et al., 2006). We are only beginning to understand its measurement and implications among those aging with HIV. Our study found that chronic non-antiretroviral polypharmacy is strongly associated with the adapted frailty-related phenotype and its domains among PLWH and uninfected veterans.

Future work is needed using longitudinal analysis to examine the temporal relationship between chronic non-ARV medication count and the aFRP to determine if indeed polypharmacy and the role of specific medication classes may be a modifiable risk factor for frailty in aging individuals with and without an HIV infection. This important work can better inform physician on deprescribing potentially inappropriate medications for individuals aging with HIV to protect them from the harmful effects of frailty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Textbox.

aFRP domains and associated survey items and answers

aFRP domain	Survey item	Answer if patient *has* the aFRP domain
Shrinking	Symptoms you might have had during the past 4 weeks: Problems with weight loss or wasting?	I have this problem and it bothers me a lot.
Exhaustion	Over the last two weeks, how often have you been bothered by: feeling tired or having little energy?	Nearly every day.
Slowness	These questions are about physical limitations you might have. Can you walk a block or more?	No, I cannot do this.
Low physical activity	These questions are about physical limitations you might have. If you want to, can you run a short distance?	No, I cannot do this.

Table 1.

Descriptive statistics of participant demographic and clinical characteristics stratified by having any aFRP domains and HIV

	Not frail, n=2794			Having any aFRP domain, n=1647		
	PLWH (%), n=1206	Uninfected (%), n=1588	p-value	PLWH (%), n=556	Uninfected (%), n=1091	p-value
Sex	--	--	<0.05	--	--	<0.05
Male	98	92	--	97	90	--
Race	--	--	<0.05	--	--	<0.05
White	24	21	--	30	25	--
Black	67	66	--	61	60	--
Hispanic	9	10	--	9	11	--
Other	1	3	--	1	4	--
Age, mean (SD)	55 (9)	56 (9)	<0.05	56 (8)	57 (9)	0.39
Number of comorbid conditions, IQR	3 (2, 4)	3 (2, 5)	<0.05	4 (2, 5)	4 (3, 6)	<0.05
Hypertension	10	48	<0.05	15	58	<0.05
Cardiovascular disease [a]	6	10	<0.05	14	17	0.08
Hepatitis C	46	27	<0.05	55	31	<0.05
Diabetes Mellitus	22	30	<0.05	30	42	<0.05
Pulmonary disease	5	8	<0.05	11	13	0.21
Liver disease [b]	46	27	<0.05	56	32	<0.05
Gastroesophageal reflux disease	3	8	<0.05	5	11	<0.05
Alcohol related diagnoses	8	14	<0.05	13	15	0.32
Drug related diagnoses	15	19	<0.05	18	18	0.90
Major Depressive Disorder	6	7	0.69	13	13	0.81
Post-Traumatic Stress Disorder	7	12	<0.05	12	19	<0.05
Bipolar disorder	3	6	<0.05	6	6	0.75
Chronic pain-related diagnoses [c]	29	46	<0.05	43	61	<0.05
FIB-4	--	--	<0.05	--	--	<0.05
<1.45	59	80	--	55	80	--
1.45 – 3.25	35	18	--	36	18	--
>3.25	6	3	--	9	2	--
Hemoglobin (g/dL), IQR	13.9 (12.8, 14.9)	14.5 (13.7, 15.3)	<0.05	13.9 (12.6, 15.0)	14.5 (13.5, 15.4)	<0.05
Estimated glomerular filtration rate (mL/min), IQR	99 (85, 116)	95 (82, 111)	<0.05	99 (84, 116)	93 (80, 108)	<0.05
Hospitalized	14	14	0.78	25	20	<0.05
Died	8	1	<0.05	16	4	<0.05
Domains of adapted frailty-related phenotype	--	--	--	--	--	--

	Not frail, n=2794			Having any aFRP domain, n=1647		
	PLWH (%), n=1206	Uninfected (%), n=1588	p-value	PLWH (%), n=556	Uninfected (%), n=1091	p-value
Shrinking	--	--	--	17	13	0.05
Exhaustion	--	--	--	32	31	0.87
Slowness	--	--	--	14	16	0.28
Low physical activity	--	--	--	74	81	<0.05
adapted Frailty-Related Phenotype	--	--	--	--	--	0.45
Pre-Frail	--	--	--	93	92	--
Frail	--	--	--	7	8	--
Viral load 50 copies/mL	72	--		74	--	0.28

[a] Cardiovascular disease is a composite of coronary artery disease/myocardial infarction, peripheral vascular disease, stroke

[b] Liver disease is a combination of end-stage liver disease, decompensated liver disease, Hepatitis B and Hepatitis C

[c] Chronic pain is composed of back, neck, temporomandibular, extremity, menstrual, rheumatoid arthritis, neuropathic and other pain

Table 2.

Chronic non-ARV medication class descriptive statistics

	Not frail, n=2794			Having any aFRP domain, n=1647		
	PLWH (%), n=1206	Uninfected (%), n=1588	p-value[a]	PLWH (%), n=556	Uninfected (%), n=1091	p-value[a]
Top 10 prescribed chronic non-ARV medications						
Antilipemics	32	38		35	45	
Angiotensin-converting enzyme inhibitors	22	27		29	34	
Antidepressants	19	23		35	35	0.93
Gastric medications	11	21		21	32	
Beta-blockers	15	21		24	30	
Non-opioid analgesics	16	21		24	36	
Calcium channel blockers	13	23		16	29	
Diuretics	15	22		18	23	
Genitourinary medications	21	23	0.26	23	23	0.75
Hypoglycemics	11	17		13	24	
Median chronic non-ARV medication count, IQR	4 (2, 7)	10 (3, 18)		6 (3, 10)	16 (8, 26)	

[a] p-value <0.05 comparing not frail and having any aFRP domain unless listed in table

Table 3.

Unadjusted and adjusted logistic regression. Output: Having any aFRP domain.

Having any aFRP domain, n=4441	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Median chronic non-ARV medication count	1.05 (1.04, 1.05)	1.04 (1.03, 1.05)
PLWH	0.67 (0.59, 0.76)	1.03 (0.89, 1.19)
Male	0.70 (0.54, 0.89)	0.64 (0.50, 0.83)
Black	0.79 (0.70, 0.90)	0.76 (0.67, 0.87)
Hepatitis C	1.17 (1.04, 1.33)	1.29 (1.13, 1.48)
Chronic pain related diagnosis	1.94 (1.72, 2.20)	1.57 (1.38, 1.79)

Table 4.

Adjusted logistic regression stratified by HIV status

Having any aFRP domain, n=4441	PLWH, n=1762		Uninfected, n=2679	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Median chronic non-ARV medication count	1.12 (1.10, 1.15)	1.11 (1.08, 1.14)	1.04 (1.03, 1.05)	1.04 (1.03, 1.04)
Male	0.86 (0.45, 1.62)	0.66 (0.35, 1.31)	0.75 (0.57, 0.98)	0.64 (0.48, 0.85)
Black	0.79 (0.64, 0.97)	0.80 (0.65, 1.00)	0.79 (0.68, 0.93)	0.75 (0.64, 0.89)
Hepatitis C	1.44 (1.18, 1.76)	1.35 (1.09, 1.67)	1.19 (1.01, 1.41)	1.22 (1.02, 1.46)
Chronic pain related diagnosis	1.87 (1.51, 2.30)	1.47 (1.18, 1.83)	1.84 (1.57, 2.15)	1.55 (1.32, 1.83)