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RESEARCH REPORT

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The association of methadone use with physical function and frailty among persons who inject drugs

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Abstract

Background and Aims: Persons who inject drugs (PWID) experience a high burden of early-onset frailty, primarily due to multifactorial causes such as infections (human immunodeficiency virus [HIV], hepatitis C virus [HCV]), substance use, and polypharmacy. Methadone, although an effective treatment for opioid use disorder, has demonstrated toxicity across several body systems that may impact or accelerate the aging process. Therefore, the purpose of this analysis was to determine the association of methadone use with frailty and physical function among PWID.

Design: This study performed a retrospective analysis from the AIDS Linked to IntraVenous Experience (ALIVE) longitudinal cohort between 2005 and 2020, using multivariable mixed effect logistic regression, adjusting for demographics, body mass index, substance use, HIV, and comorbidities.

Setting: Baltimore, Maryland, United States.

Participants: Adult participants (≥18 years) were recruited into the ALIVE cohort if they reported a history of or current injection drug use. Our study included 2153 participants with 13 909 person-years of follow-up.

Measurements: Methadone usage, whether prescribed or non-medical, was self-reported by participants during study follow-up. The primary outcome measurement was frailty as defined by the Fried frailty phenotype. Physical function was measured using grip strength and 4-m gait speed.

Findings: At baseline, 883 were currently using methadone. Median age was 48 (interquartile range: 42, 53) years; 81% were Black, 34% female, 80% had incomes <$5000, and 31% were living with HIV. Methadone use was associated with 25% higher odds of frailty (95% confidence interval [CI]: 1.09, 1.43). This difference suggested that the odds

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of frailty among individuals using methadone at age 50 were comparable to those not using methadone at age 54. Methadone use was associated with lower average grip strength [−0.71 kg (95% CI: −0.94, −0.48)], but not slower gait speed.

Conclusions: Among persons who inject drugs, those using methadone appear to be more likely to experience frailty at an earlier age compared with those not using methadone. Early screening for frailty and other geriatric conditions may be warranted among individuals with active methadone use in this population.

KEYWORDS
aging, frailty, functional impairment, methadone, opioid agonist therapy, persons who inject drugs, physical function

INTRODUCTION

Opioid use disorder remains a prevalent and devasting public health crisis despite the availability of medication-assisted treatment options [1, 2]. Methadone maintenance treatment (MMT) is an effective medication-assisted treatment for opioid dependence and reduces risk of overdose, one of the leading causes of death among persons who inject drugs (PWID) [3–5]. Additionally, MMT has been associated with reduced hepatitis C virus (HCV) and HIV transmission among PWID, and has been associated with antiretroviral therapy (ART) adherence among PWID with HIV [6–8]. Older adults now comprise a greater proportion of those receiving MMT, and this proportion is expected to rise [9]. However, the long-term use of methadone has been linked to a significantly higher comorbidity burden, which may have subsequent consequences for other age-related conditions, such as frailty [10, 11].

Persons who inject drugs (PWID), independent of drug type, are at an increased risk for frailty, a condition defined as a state of increased vulnerability to adverse clinical outcomes [12, 13]. Frailty is associated with an increased risk for all-cause mortality, hospitalizations and heightened comorbid disease among multiple populations, including PWID [14]. PWID have a higher prevalence of risk factors for frailty, including HIV, lower educational attainment and number of comorbid conditions [15]. Chronic methadone use may heighten this risk owing to its known toxic effects exerted on other body systems (i.e. central nervous system, cardiovascular system) that may contribute to the development of frailty [16, 17].

Given the potential for compounding complications among PWID chronically using methadone, monitoring for the early onset of age-associated syndromes such as frailty may be a necessary component of their long-term care [13]. The early identification of frailty is a key factor for the initiation of preventive measures. However, to date, no study has examined whether chronic methadone use is associated with the premature onset of frailty, pre-frailty or poor physical function. Therefore, the purpose of this analysis was to longitudinally examine the impact of methadone use on frailty and physical function in a population of PWID.

METHODS

Study population

Our study population is from the AIDS Linked to the Intravenous Experience (ALIVE) cohort. This community-based cohort, initiated in 1988, recruits people with a history of injection drug use. Participants have been followed on a semi-annual basis. We included participants with at least two study visits from July 2005 to February 2020. Detailed information for study design, enrollment and measurement collection has been documented previously [18]. All participants provided written informed consent, and the study was approved by the Johns Hopkins Institutional Review Board. The analysis was not preregistered and therefore all results should be considered exploratory.

Data collection

Study participants receive a physical examination, clinical interview and laboratory specimen collections every 6 months after recruitment. We obtained information from the first (baseline) visit and past 6 months for the following variables from the data repository: age, sex, race, education level, income, working status, body mass index (BMI), HIV infection, depressive symptoms, comorbidities, and use of alcohol, cigarettes, cocaine and opiates. HIV status was defined as HIV-1 antibody positive with Western blot confirmation. Depression was measured using the Center for Epidemiologic Studies Depression Scale (CES-D) and defined as having a score of ≥23. Comorbidities of heart disease, renal disease, lung disease, liver disease, diabetes, stroke, obesity and cancer were self-reported. Comorbidity status was grouped into three categories: having no comorbidities, one or two comorbidities, or three or more comorbidities. Hazardous alcohol use was defined through the Alcohol Use Disorder Identification Test (AUDIT) [19].

Methadone use

Self-report of any methadone use (prescribed or illicit use) and prescribed methadone use in the past 6 months were recorded at semi-

annual visits. We defined exposure to methadone use as: (i) time-varying any methadone use; (ii) time-varying prescribed methadone use; and (iii) time-varying cumulative methadone use. For cumulative methadone use, we summed the total time of using any methadone and the total time of not on methadone up to each visit for each participant as a time-varying variable.

Physical function (grip strength and gait speed)

Grip strength was assessed using a Jamar dynamometer (Sammons Preston, Bolingbrook, IL, USA) [20]. Gait speed was measured by time to walk 4 m at a comfortable pace. Both gait speed and grip strength are measured twice, and the average of the measurements is used.

Frailty definition and classification

Frailty was defined using the five original Fried criteria [21]: weight loss, exhaustion, physical inactivity, low hand grip strength and slow walking speed.

We defined weight loss as losing ≥5% of body weight since the last visit. Participants who reported that 'everything was an effort' or 'could not get going for moderate or most of the time in the past week' met the criteria for exhaustion. Those that reported being limited 'a lot to vigorous activities such as lifting heavy objects, running or participating in strenuous sports' were classified as having low physical activity. Low hand grip strength was defined as performing in the lowest 20th percentile by sex assigned at birth and BMI, and slow walk speed as the lowest 20th percentile by gender and median height. The sum of the frailty score was categorized as: ≥3, frail; 1 or 2, pre-frail; and 0, robust. We also classified the two-level frailty outcome into: 'yes' or 'no' frailty (i.e. pre-frailty and robust vs frailty).

Statistical analysis

We compared baseline characteristics of the participants by methadone use in the past 6 months. The longitudinal patterns of methadone use were explored graphically (Figure 1). We used multilevel mixed-effects logistic regression with random intercepts for participants to evaluate the relationship between any methadone use and the two-level frailty outcome (yes vs no), random-effects multinomial logit model for the three-level frailty outcome (robust vs pre-frail vs frail) and multi-level mixed-effects linear regression for trajectories of gait speed and grip strength. We used age as the timescale in the model to estimate the predicted probability of frailty and the decline in physical function, both as a function of age. All models were controlled for demographics (age, sex, race, education, income and employment), BMI, alcohol use, substance use (cigarette, cocaine, opiates), HIV infection, underlying comorbidity and depressive symptoms. We explored changes of methadone use patterns between visits by creating four use patterns: continued use, never use, started use and discontinued use, by comparing methadone use between current and previous visits. The association of the odds of frailty and methadone use patterns between visits were assessed using multivariable mixed-effects logistic regression with random intercepts. We performed an E-value analysis to assess the potential impact of unmeasured confounding factors. We further explored sex differences in the association in a sex-stratified analysis. Covariates were selected based on previous literature, preliminary data analyses and change in magnitude of effects in the association of interest. All statistical tests were conducted in STATA 18 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study population

Table 1 presents the baseline characteristics of the study participants. Among the 2153 participants included at baseline, 883 (41%) reported exposure to any use of methadone in the past 6 months and 676 (31%) were using prescribed methadone in the past 6 months. Overall, the median age was 48.1 years old (interquartile range, IQR = 42.2–53.1 years), 34% were female and 81% were Black. Most had an income of <$5,000 per year (80%) and were not actively working (80%). Those that were on methadone were more likely to be obese. A majority reported current cigarette smoking (84%), having no or mild depressive symptoms (73%) and 31% were living with HIV. About 25% of the participants reported three or more comorbidities, and those that were on methadone had a higher proportion of having more comorbidities. The baseline characteristics of participants were similar when we stratified participants by any methadone use or by only prescribed methadone use (Table S1).

Among participants who reported any use of methadone (representing a total of 1373 ALIVE participants over the entire course of the follow-up period), the patterns and trajectories of methadone use for each individual throughout the study follow-up time is presented in Figure 1. The majority of these participants (n = 776, 57%) reported using methadone in over 50% of their study visits, while 22% reported using it in less than 25% of their visits and 21% reported using it in 25%–50% of their visits. We observed an uptick in methadone use during study visits preceding the end of the observational window, particularly among participants who reported methadone use in more than 25% of their study visits.

Association of methadone use and odds of frailty

Any methadone use and cumulative (every additional year) methadone use were associated with increased odds of frailty (Table S2). Using any methadone was associated with 18% higher odds of being

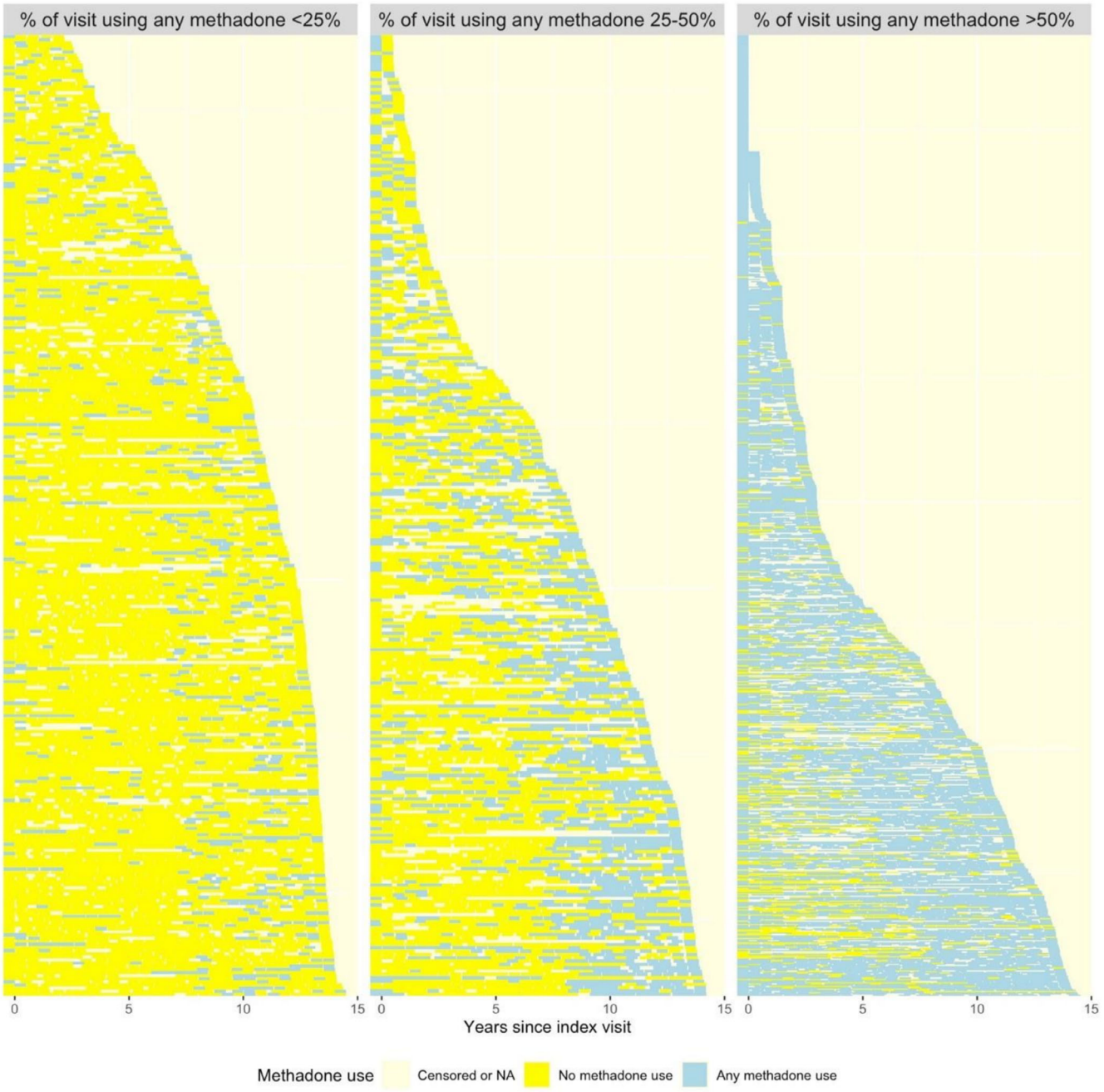

FIGURE 1 Pattern of methadone use among participants reporting any use of methadone across study follow-up in the ALIVE cohort. Any methadone use includes methadone use through prescription and the non-medical use of methadone.

frail versus non-frail (OR = 1.18, 95% CI = 1.03–1.35), compared with not using methadone. Figure 2 demonstrated that among those who use methadone, the predicted probability of frailty at age 50 years was comparable with the probability of being frail at age 54 years among those not using methadone. Current use of opiates (OR = 1.18, 95% CI = 1.10–1.38), having HIV (OR = 1.28, 95% CI = 1.05–1.56), having three or more comorbidities (OR = 1.95, 95% CI = 1.63–2.32) and having severe depression (OR = 3.08, 95% CI = 2.69–3.52) were also related to higher risk of frailty, when considering frailty as two categories (robust vs frail). Each additional year of any methadone use was related to 4% higher odds for frailty (OR = 1.04, 95% CI = 1.01–1.07). In a separate analysis, we assess the association of time-updated change in methadone use and odds of frailty. Compared with participants who continued to use methadone, those who discontinued methadone from the previous visit had a non-significant 5% reduction in risk for frailty compared with current users (OR = 0.95, 95% CI = 0.76–1.19; Table S3). We found no difference in the association between any methadone use and frailty risk when comparing males and females (Table S4). In the preliminary analyses, no statistically significant interaction between age and

TABLE 1 Participant characteristics on study baseline, ALIVE cohort, 2005–2020.

	Any methadone use		
	Overall (*n* = 2153)	**Yes (*n* = 883)**	**No (*n* = 1270)**
Age, median (IQR)	48.1 (42.2–53.1)	48.1 (41.0–53.4)	48.1 (43.1–52.9)
Sex (female), *n* (%)	722 (33.5)	374 (42.4)	348 (27.4)
Black race, *n* (%)	1746 (81.1)	642 (72.7)	1104 (86.9)
Education (high school), *n* (%)	962 (44.8)	389 (44.2)	573 (45.2)
Income (<$5,000 per year), *n* (%)	1664 (79.7)	704 (81.9)	960 (78.2)
Work status, *n* (%)	447 (20.9)	135 (15.4)	312 (24.7)
BMI, *n* (%)			
Normal	920 (44.6)	341 (39.8)	579 (48.1)
Overweight	670 (32.5)	278 (32.5)	392 (32.5)
Obese	471 (22.9)	237 (27.7)	234 (19.4)
AUDIT, *n* (%)			
Low risk	945 (44.1)	357 (40.6)	588 (46.5)
Moderate use	500 (23.3)	233 (26.5)	267 (21.1)
Hazardous use	700 (32.6)	289 (32.9)	411 (32.5)
Cigarette use, *n* (%)	1806 (84.3)	783 (89.1)	1023 (81.0)
Cocaine use, *n* (%)	1130 (52.7)	554 (63.0)	576 (45.5)
Opiate use, *n* (%)	1178 (54.9)	576 (65.5)	602 (47.6)
HIV, *n* (%)	658 (30.6)	230 (26.1)	428 (33.7)
Comorbidity group, *n* (%)			
No comorbidities	920 (44.1)	324 (38.5)	596 (47.9)
1–2 comorbidities	641 (30.7)	268 (31.9)	373 (30.0)
≥3 comorbidities	524 (25.1)	249 (26.6)	275 (22.1)
Depressive symptoms			
No or mild depressive symptoms	1570 (73.2)	560 (63.6)	1010 (79.8)
Severe depressive symptoms	575 (26.8)	320 (36.4)	255 (20.2)

BMI = body mass index (kg/m^2); AUDIT = Alcohol Use Disorder Identification Test. We classified alcohol use as: 0–7, low risk; 8–15, moderate use; and ≥16, hazardous use.
The comorbidity group includes conditions of heart disease, renal disease, lung disease, liver disease, diabetes, neurocognitive dysfunction and cancer. Depression: no or mild depression with Center for Epidemiologic Studies Depression Scale (CES-D) score of <23; severe depression with CES-D score of ≥23.

methadone use was detected in relation to the odds of frailty across any of the models, suggesting the odds of frailty did not increase more steeply with age among those who use methadone. Therefore, the final models did not include the interaction between age and methadone use.

When considering frailty in three categories (robust, pre-frail and frail), using any methadone was associated with 12% higher odds of being pre-frail compared with robust (OR = 1.12, 95% CI = 1.01–1.23), and 26% higher odds of being frail compared with robust (OR = 1.26, 95% CI = 1.07–1.48) (Table S4). Figure 3 and Table S5 shows the model-predicted marginal probability of being robust, pre-frail and frail by methadone use, using age as the timescale. Participants who were not using any methadone had a consistently higher probability of being robust at all ages, while participants who were using any methadone had a consistently higher probability of being frail. The probability of being pre-frail increased with age among people with and without methadone use but was higher among people using methadone up to the age of 50 years, and then was similar to those not using methadone over the age of 50 years.

Association of methadone use and physical function (grip strength and gait speed)

Table 2 presents the association of methadone use with gait speed and grip strength. Methadone use was associated with 0.69 kg decreased grip strength (95% CI = −0.92 to −0.46 kg). The association between methadone use and gait speed was not statistically significant. When stratified by sex, we found only a significant relationship between any methadone use and grip strength among males but not females. The difference in grip strength is only about one-third in

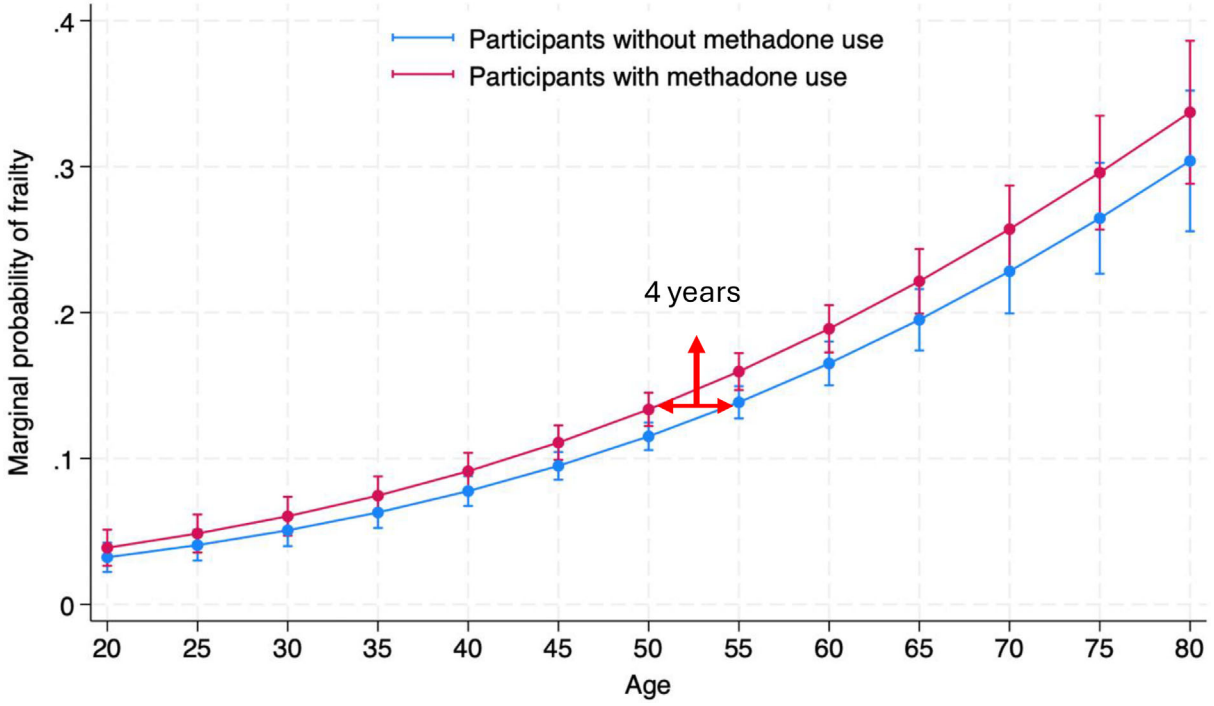

FIGURE 2 Predicted margins of age-related odds of frailty by any methadone use in the ALIVE cohort (2005–2020). Marginal probabilities were estimated based on multi-variable multinomial mixed-effects model controlled for age, sex, race, education, income, work status, BMI, alcohol use, cigarette use, cocaine use, opiate use, HIV status and comorbidity counts. BMI = body mass index (kg/m^2); AUDIT = Alcohol Use Disorder Identification Test. We classified alcohol use as: 0–7, low risk; 8–15, moderate use; and ≥16, hazardous use. The comorbidity group includes conditions of heart disease, renal disease, lung disease, liver disease, diabetes, neurocognitive dysfunction and cancer. Depression: no or mild depression with Center for Epidemiologic Studies Depression Scale (CES-D) score of <23; severe depression with CES-D score of ≥23.

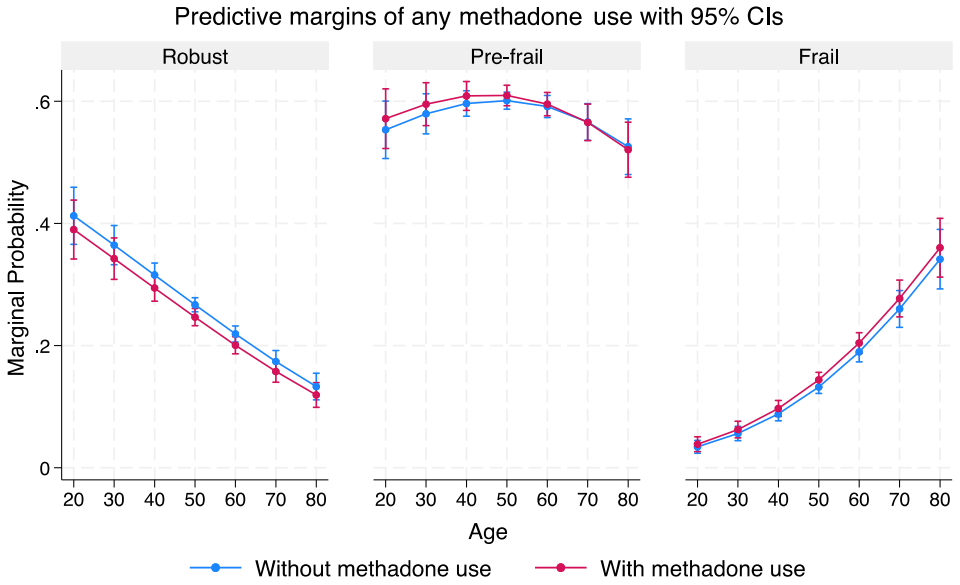

FIGURE 3 Predicted margins of age-related odds of robust, pre-frail and frail by any methadone use in the ALIVE cohort (2005–2020). Marginal probabilities were estimated based on multi-variable multinomial mixed-effects model controlled for age, sex, race, education, income, work status, BMI, alcohol use, cigarette use, cocaine use, opiate use, HIV status and comorbidity counts. BMI = body mass index (kg/m^2); AUDIT = Alcohol Use Disorder Identification Test. We classified alcohol use as: 0–7, low risk; 8–15, moderate use; and ≥16, hazardous use. The comorbidity group includes conditions of heart disease, renal disease, lung disease, liver disease, diabetes, neurocognitive dysfunction and cancer. Depression: no or mild depression with Center for Epidemiologic Studies Depression Scale (CES-D) score of <23; severe depression with CES-D score of ≥23.

TABLE 2 The association between any methadone and physical function in the ALIVE cohort (2005–2020).

	Grip strength		Walk speed	
	OR	*P*	OR	*P*
Any methadone	−0.69 (−0.92, −0.46)	<0.001	−0.0010 (−0.0080, 0.0061)	0.793
Age	−0.38 (−0.40, −0.36)	<0.001	−0.0029 (−0.0035, −0.0022)	<0.001
Sex	−14.82 (−15.49, −14.16)	<0.001	−0.0656 (−0.0831, −0.0481)	<0.001
Black race	3.61 (2.77, 4.45)	<0.001	−0.0571 (−0.0796, −0.0346)	<0.001
Education (high school)	1.35 (0.72, 1.98)	<0.001	0.0197 (0.0033, 0.0361)	0.019
Income (<$5,000)	0.01 (−0.20, 0.22)	0.919	−0.0039 (−0.0104, 0.0027)	0.246
Work status	0.26 (0.002, 0.52)	0.048	0.0188 (0.0107, 0.0270)	<0.001
BMI				
Normal				
Overweight	1.68 (1.42, 1.93)	<0.001	−0.0006 (−0.0085, 0.0072)	0.878
Obese	2.89 (2.55, 3.23)	<0.001	−0.0168 (−0.0272, −0.0063)	0.002
AUDIT				
Low risk				
Moderate use	0.18 (−0.06, 0.43)	0.147	0.0020 (−0.0058, 0.0097)	0.615
Hazardous use	0.04 (−0.25, 0.32)	0.79	0.0026 (−0.0062, 0.0114)	0.566
Cigarette	0.47 (0.17, 0.76)	0.002	−0.0078 (−0.0171, 0.0014)	0.096
Cocaine	−0.17 (−0.43, 0.08)	0.18	0.0070 (−0.0009, 0.0148)	0.084
Opiate	−0.30 (−0.54, −0.05)	0.018	0.0024 (−0.0053, 0.0100)	0.549
HIV	−1.72 (−2.32, −1.12)	<0.001	−0.0176 (−0.0340, −0.0013)	0.034
Comorbidity group				
No comorbidities				
1–2 comorbidities	0.42 (0.18, 0.67)	0.001	0.0042 (−0.0034, 0.0119)	0.280
≥3 comorbidities	0.37 (0.07, 0.66)	0.015	−0.0078 (−0.0170, 0.0013)	0.092
Depression				
No or mild depression				
Severe depression	−0.46 (−0.70, −0.23)	<0.001	−0.0048 (−0.0121, 0.0025)	0.195

BMI = body mass index (kg/m^2); AUDIT = Alcohol Use Disorder Identification Test. We classified alcohol use as: 0–7, low risk; 8–15, moderate use; and ≥16, hazardous use.
The comorbidity group includes conditions of heart disease, renal disease, lung disease, liver disease, diabetes, neurocognitive dysfunction and cancer. Depression: no or mild depression with Center for Epidemiologic Studies Depression Scale (CES-D) score of <23; severe depression with CES-D score of ≥23.

females compared with males (Table S6). However, the results for gait speed and any methadone use were consistent for males and females (Table S7).

Sensitivity and E-value analysis

Results were similar when comparing effect size in models on prescribed methadone use and any methadone use (Tables S8–S11). After accounting for a comprehensive set of covariates, including demographics (age, sex, race, education, income, employment), BMI, alcohol use, substance use (cigarettes, cocaine, opioids), HIV status, comorbidity burden and depressive symptoms, the E-value for the association between methadone use and frailty was 1.51 (Table S12).

DISCUSSION

The present study examined the association between methadone use, frailty and physical function among participants in the ALIVE cohort. First, we found that methadone use, either through prescription or illicit use, was associated with 18% higher odds of frailty. Among participants taking methadone, the odds of frailty among individuals at age 50 years were comparable with those who were not using methadone at age 54 years. When examining cumulative exposure to methadone, each additional year of methadone use resulted in 4% higher odds of frailty. These associations were independent of other substance use and comorbidity burden, highlighting the adverse outcomes of the long-term use of methadone as a treatment or exposure.

To our knowledge, this is the first longitudinal analysis to provide evidence that there is an association between chronic methadone use and frailty, with compounding risk over time, among those chronically using methadone. Prior cross-sectional work identified a 16.6% and 24.2% prevalence of frailty and pre-frailty, respectively, among patients using any type of opioid agonist therapy using the FRAIL scale [22]. Our finding that methadone use specifically is associated with a higher odds of frailty is consistent with previous literature on the development of geriatric conditions and comorbidities among adults receiving MMT. A recent cross-sectional study found a higher prevalence of self-reported geriatric conditions (i.e. falls, mobility impairment, urinary incontinence) among adults in outpatient methadone programs compared with US adults who are not seeking treatment in outpatient methadone programs [13]. Similarly, patients on MMT in primary care settings demonstrated substantially higher rates of chronic disease and multi-morbidity than age-matched controls, even after drug-related infections such as hepatitis B/C and HIV were controlled for [11].

Despite the increased risk of frailty, no substantial differences were seen in the objective measures of physical function between those using methadone and those not using methadone. Gait speed was similar, and although grip strength statistically differed between the groups, the difference was small (0.69 kg) and not within the range that is considered clinically relevant (5.0–6.2 kg) [23]. Differences between the groups may be less pronounced because grip strength and gait speed were already decreased among the entire cohort of PWID compared with epidemiologically similar populations who do not inject drugs. Additionally, among PWID there are other contributing factors, beyond physical function, that determine frailty risk. For example, the comorbidity burden is high in the ALIVE cohort, with 25% of participants having three or more comorbid conditions. Poorly controlled HIV and chronic inflammation account for the substantial risk of frailty and mortality among ALIVE participants [24]. Additionally, weight fluctuation and weight loss are also common within the cohort, which may impact the 'unintentional weight loss' criteria of the Fried frailty phenotype.

Underlying physiological mechanisms may explain the link between chronic methadone use and frailty. MMT is hypothesized to inhibit the hypothalamic–pituitary–gonadal axis, leading to hypogonadism [25]. The suppression of sex hormones is thought to explain the decreased bone mineral density seen among those on MMT and may contribute to the earlier progression of frailty given the association of low bone density and frailty [26–28]. Sex hormones are also essential for the development and maintenance of muscle mass, and loss of muscle mass is associated with the development of frailty and decline in physical function [29].

The finding of an earlier onset of frailty in this population has several clinical implications. Our findings suggest that even substance use treatment may have additional impacts on physical health in this already high-risk population. These findings are not to discourage individuals from pursing harm reduction treatments, including prescribed MMT, which are critical for reducing the risk of fatal and non-fatal overdose. Rather, we underscore the importance of early screening and intervention for frailty and physical function among individuals receiving such treatment and the integration of clinical models designed to intervene and prevent further progression of aging-related conditions [30]. The incorporation of a geriatric-based approach to care at outpatient treatment clinics may help attenuate or prevent complications associated with aging, such as hospitalization, loss of independence and decreased quality of life [13]. Additionally, our findings encourage the consideration of more optimized long-term strategies for managing substance use disorders. Further research is also needed to evaluate alternative treatment options with potentially fewer adverse physical effects. Other opioid treatment, such as buprenorphine, which has a more favorable effect on the gonadal axis, may provide an alternative to reduce long-term impact [31].

A few limitations should be noted. First, given the PWID population, there was loss to follow-up in this patient population, which resulted in 16.2% of overall missing data (7.7% for gait speed, 11.5% grip strength). We applied mixed-effect models with the maximum-likelihood estimate in our longitudinal analyses, which can better account for missing values compared with other modeling techniques, thereby maximizing the use of available data. The amount of missingness is considered acceptable, so we were able to provide a robust estimate despite the missing data [32–35]. Second, we were unable to obtain data on dose of methadone use during each visit; therefore, our analysis has the complication of a prevalent exposure analysis without more detailed information regarding methadone frequency and dosage. Third, although we used the Fried phenotype to define frailty, there is still no clear consensus regarding the optimal or gold-standard definition of frailty [36, 37]. Finally, our analysis was unable to incorporate the possible feedback loop between past frailty status and current healthcare-seeking behaviors. Despite these limitations, our study has several strengths. The ALIVE cohort has a large sample size with over 30 years of longitudinal data on a population that is typically difficult to reach and retain in clinical trials. Although indication bias is typically a concern for methadone use in other population-based cohorts, all participants in the ALIVE cohort were recruited based on current or past injection drug use. As a result, participants had comparable exposure to opioid use and, consequently, a similar indication for methadone treatment. We were also able to use longitudinal frailty data in combination with longitudinal methadone use assessment (from 2005 to 2020) to inform our findings. Furthermore, we conducted an E-value analysis to assess the impact of unmeasured confounding variables. Notably, the E-value for methadone use was more robust than that observed for several demographic and behavioral factors (e.g. age, education, income, cigarette use, alcohol use and cocaine use), and was comparable with that of opioid use (E-value = 1.6). Higher E-values were observed for established predictors of frailty, including sex, race, BMI, depression and comorbidity count. This suggests that the association between methadone use and frailty is reasonably robust to unmeasured confounders. These findings fill a significant gap in the literature, highlighting the potential risks associated with prolonged methadone use among PWID. This knowledge may guide risk assessment and motivate the development of new opioid treatment strategies in the future.

In conclusion, we found that methadone use, both prescribed and non-prescribed, was associated with a higher risk for frailty among PWID. As methadone continues to be an effective cornerstone treatment for preventing overdose and reducing mortality, there is an important balance between the positive impact of methadone and its long-term side effects. The potential side effects from chronic methadone use underscore the need for further research into the optimal length of time an individual should be on methadone to achieve their goal of opioid cessation or reduce the frequency of opioid use. Findings from the present study suggest that individuals on long-term MMT may benefit from increased monitoring for aging-associated conditions, such as frailty. Future research should also investigate the impact of MMT on muscle mass or muscle quality, and the impact of other opioid agonist therapies, such as buprenorphine, on frailty and physical function.

AUTHOR CONTRIBUTIONS

Grace L. Kulik: Writing—original draft (equal); writing—review and editing (equal). **Hsing-Yu Hsu:** Formal analysis (equal); writing—original draft (equal). **Jacqueline Rudolph:** Writing—review and editing (equal). **Yutong Jiang:** Formal analysis (equal); writing—review and editing (equal). **Kristine M. Erlandson:** Writing—review and editing (equal). **Damani A. Piggott:** Project administration (equal); writing—review and editing (equal). **Shruti Mehta:** Writing—review and editing (equal). **Jeremy D. Walston:** Project administration (equal); writing—review and editing (equal). **Gregory Kirk:** Project administration (equal); writing—review and editing (equal). **Todd T. Brown:** Funding acquisition (equal); project administration (equal); writing—review and editing (equal). **Jing Sun:** Formal analysis (equal); funding acquisition (equal); project administration (equal); supervision (equal); writing—review and editing (equal).

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DECLARATION OF INTERESTS

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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