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Original article

Illicit drug use is associated with lower bone mineral density and bone strength

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ABSTRACT

Objectives: To evaluate the association of illicit drug use with bone mineral density (BMD) and hip geometric parameters at the narrow neck.
Methods: This is a cross-sectional matched cohort study conducted in the Hong Kong Chinese population. Associations with illicit drug use were estimated using linear regression for BMD (lumbar spine and femoral neck) and hip geometrical parameters (cross-sectional area [CSA], cross-sectional moment of inertia [CSMI], section modulus [SM], average cortical thickness [ACT] and BMD at the narrow neck) after adjusting for age, body mass index (BMI), smoking status, drinking status, physical activity, and history of antipsychotic and antidepressant use. Mean difference and 95% confidence intervals (95% CI) were calculated between 108 illicit drug users and 108 controls using an adjusted linear model and cluster-robust standard errors after matching by age and sex. The false discovery rate was used to correct for multiple testing.
Results: Illicit drug users had a significantly lower BMD (g/cm^2) at the lumbar spine (mean difference: −0.062; 95% CI: −0.108 to −0.015), and femoral neck (mean difference: −0.058; 95% CI: −0.106 to −0.010) in the fully adjusted model. Illicit drug users also had a significantly lower CSA (mean difference: −0.238 cm^2; 95% CI: −0.462 to −0.013), ACT (mean difference: −0.018 cm; 95% CI: −0.030 to −0.006) and BMD (mean difference: −0.070 g/cm^2; 95% CI: −0.128 to −0.012) at the narrow neck.
Conclusions: Illicit drug use is associated with lower BMD and bone strength. Future studies evaluating the risk of illicit drug use with fragility fracture are warranted.

1. Introduction

Illicit drug use has previously been reported to be associated with adverse health, societal and personal consequences [1,2]. The overall trend of illicit drug use has been increasing globally and illicit drug use may result in unwanted health outcomes, such as mental health issues, renal and cardiovascular diseases [3,4]. Although much research has been performed to investigate these adverse health outcomes, the relationship of illicit drug use with other body systems, such as the skeletal system, is less understood.

Osteoporosis is a prevalent disease affecting more than 300 million people worldwide. Patients with osteoporotic fractures are not only associated with increased morbidity and mortality, but also increased risk of dependency, immobility, and institutionalization. Thus, poor bone health poses a huge burden to individuals, caregivers, and society [5]. As such, understanding the relationship between illicit drug use and bone health is clinically important. Previously, a few commonly used illicit drugs were reported to be associated with reduced bone mineral density (BMD) [6–10]. However, some of these studies lacked a control group [8], used other substance users as controls [6], or had a small

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sample size [7]. Using the BMD T-scores in defining osteoporosis in young subjects was common in previous studies [8–10], but it is not recommended according to international guidelines [11]. In addition to BMD, other bone-related parameters, such as hip geometry, were not studied.

In this study, we aim to evaluate the association of illicit drug use with BMD and hip geometrical parameters at the narrow neck among 108 illicit drug users and 108 non-users, constituting one of the largest samples of illicit drug users to date.

2. Methods

2.1. Participants

Illicit drug users (N = 108) included current drug users and users with a history of illicit drug use who were recruited via referral from the substance abuse clinic in the Hong Kong West Cluster as well as various local drug treatment centers and social rehabilitation service centers in Hong Kong. Non-users were participants from the Hong Kong Osteoporosis Study (HKOS) [12]. Among the 1390 participants from the in-person follow-up study of the HKOS [12], those with missing data were excluded [smoking status (N = 4), drinking status (N = 13), BMI (N = 3), BMD (N = 6), hip geometric parameters (N = 13)]. Out of a total of 1362 participants who fulfilled the inclusion criteria, 108 individuals were chosen as controls for the final analysis. These control participants were selected after age and sex matching with illicit drug users. Nearest neighbor matching was done with an exact specification for sex using the R package MatchIt [13]. All participants were of Chinese ethnicity. Physical measurements were assessed by a trained research assistant or nurse. Basic demographic information and lifestyle factors were collected using a structured questionnaire. Records of prescription were obtained via linkage to the territory-wide electronic medical record database, Clinical Data Analysis and Reporting System (CDARS), which is managed by the Hong Kong Hospital Authority. The study has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB Reference Number UW 15–236 and UW 18–401) and all participants gave informed consent for participating in the study.

2.2. Illicit drug use assessments

For illicit drug users, medication and drug abuse history was obtained from a detailed interview by a trained registered pharmacist. Given that illicit drug users commonly used more than just 1 illicit drug, only the most frequently used drug reported by each individual, based on their self-reported history of illicit drug use, was considered in the analysis. Drug categories were defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [14].

2.3. Skeletal health assessments

BMD at the lumbar spine and femoral neck was measured using Hologic Discovery A dual energy X-ray absorptiometry (DXA) (Waltham, MA, USA) as reported previously [12]. Hip geometry at the narrow neck was analyzed using hip structural analysis. Five hip geometric parameters at the narrow neck, cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), section modulus (SM), average cortical thickness (ACT), and BMD, were studied because these parameters were shown to be highly correlated with parameters measured by quantitative computed tomography (QCT) [15] or were predictors of hip fracture risk [16]. DXA measurements were carried out by trained technicians using a standardized protocol. Quality control scans were conducted daily using the spine phantom to ensure consistent measurement.

2.4. Covariates

A structured questionnaire was used to obtain basic demographic information as well as history of drinking and smoking. Drinking and smoking status was categorized into current-, ex-, and never-smoker or drinker. Physical activity was evaluated using the modified Yale Physical Activity Survey (YPAS) questionnaire [17], which has been validated in the Chinese population previously [18]. The intensity of each physical activity was expressed as a metabolic equivalent (MET), defined as the energy expenditure at a resting metabolic rate. Physical activities with 3–6 METs are considered moderate, and those > 6 METs are considered vigorous [19]. Based on the total duration (in minutes) spent on each physical activity per week as well as the number of sessions the activity was conducted per week, the study participants were categorized as physically inactive, minimally active, or active. Physically active was defined by either 1 of the following 2 definitions [1]: having vigorous physical activity, with at least 3 sessions and a total duration of at least 180 min per week; or [2] having moderate physical activity, with at least 5 sessions and a total time of at least 300 min per week. Physically inactive was defined as those with no reported leisure time physical activity. Moderately active was defined as those who were not inactive but did not meet the criteria to be considered physically active. Use of any antipsychotic and antidepressant listed in chapters 4.2.1 and 4.3 of the British National Formulary respectively was retrieved from CDARS prescription records and dispensing records.

2.5. Statistical analysis

Demographic characteristics are expressed as frequencies for categorical variables and mean ± standard deviation (SD) for continuous variables in the descriptive statistics. The differences between controls and illicit drug users were compared by *t*-test (for continuous variables) or chi-square test (for categorical variables). The association of illicit drug use with the outcomes was evaluated using weighted linear regression. As an age- and sex-matched cohort was used, the R package sandwich [20] was used to calculate cluster-robust standard errors and 95% confidence intervals, accounting for pair membership in the cohort. The outcome model was adjusted for age and BMI in model 1, followed by further adjustment for physical activity, smoking, and drinking status in model 2 and further adjustment for antidepressant and antipsychotic use within one year before the date of skeletal health assessments in model 3. Age was further adjusted to account for residual confounding since age was not exactly matched. The false discovery rate (FDR) was used to correct for multiple testing and an FDR < 0.05 was considered statistically significant. Analyses were also conducted to investigate the association of each illicit drug category with different outcomes using the fully adjusted model. The analyses were repeated by adjusting for antidepressant and antipsychotic use within 5 years before the date of skeletal health assessment as the sensitivity analysis. This was done as some effects of antidepressants and antipsychotics are known to persist long after the cessation of treatment [21]. We also conducted a subgroup analysis by drug category. Using the control group as a reference, weighted linear regression was used to evaluate whether any individual drug category was associated with the outcomes using the fully adjusted model (model 3). Given the exploratory nature of the subgroup analysis, corrections for multiple testing were not applied. All analyses were performed using R version 4.1.0 (www.R-project.org).

3. Results

3.1. Demographics and descriptive statistics

The most used illicit drugs among the study participants are shown in Table 1. The most used drug among the study participants was heroin (N = 53, 49.1%), followed by methamphetamine (N = 19, 17.6%) and cannabis (N = 8, 7.4%). Table 2 shows the descriptive statistics and the

Table 1
Types of illicit drugs used by the illicit drug users (N = 108).

Category	Drug	Count	Percentage
Cannabis	Cannabis/Marijuana	8	7.4
Hallucinogens	Ketamine	5	4.6
Opioids	Heroin	53	49.1
	Methadone	3	2.8
	Opiates/Opium	1	0.9
Sedatives, hypnotics or anxiolytics	Midazolam	2	1.9
Stimulants	Cocaine	1	0.9
	Methamphetamine	19	17.6
	Methylenedioxymethamphetamine	2	1.9
Others	Amyl nitrite	1	0.9
	Gamma hydroxybutyric Acid	1	0.9
	Others	4	3.7
	Unknown	8	7.4

Table 2
Descriptive characteristics and Demographics of the study participants (N = 216).

	Control (N = 108)	Iliicit drug users (N = 108)	P-value
Age, yr	51.19 (12.18)	49.67 (14.28)	0.401
Female, N	14 (13.0)	14 (13.0)	1.000
BMI, kg/m^2	23.29 (3.02)	23.73 (4.17)	0.370
Smoking status, N			<
Non-smoker	92 (85.2)	17 (15.7)	0.001
Ex-smoker	9 (8.3)	16 (14.8)	
Current-smoker	7 (6.5)	75 (69.4)	
Drinking status, N			<
Non-drinker	54 (50.0)	21 (19.4)	0.001
Ex-drinker	10 (9.3)	35 (32.4)	
Current-drinker	44 (40.7)	52 (48.1)	
Physical activity, N			0.010
Active	15 (13.9)	8 (7.4)	
Moderate	72 (66.7)	60 (55.6)	
Inactive	21 (19.4)	40 (37.0)	
BMD, g/cm^2			
Lumbar spine	1.00 (0.17)	0.98 (0.14)	0.285
Femoral neck	0.79 (0.15)	0.75 (0.11)	0.045
Hip geometry at the narrow neck			
Cross-sectional area, cm^2	3.22 (0.66)	3.07 (0.45)	0.055
Cross-sectional moment of inertia, cm^4	3.19 (1.01)	3.03 (0.86)	0.210
BMD, g/cm^2	0.95 (0.18)	0.91 (0.13)	0.045
Average cortical thickness, cm	0.18 (0.04)	0.17 (0.03)	0.004
Centroid Position	0.45 (0.03)	0.45 (0.02)	0.203
Section Modulus, cm^3	1.61 (0.42)	1.54 (0.32)	0.170
Antipsychotic use			
Within 1 year prior to skeletal assessment	2 (1.9)	20 (18.5)	< 0.001
Within 5 years prior to skeletal assessment	2 (1.9)	24 (22.2)	< 0.001
Antidepressant use			
Within 1 year prior to skeletal assessment	2 (1.9)	34 (31.5)	< 0.001
Within 5 years prior to skeletal assessment	2 (1.9)	41 (38.0)	< 0.001

Data are presented as mean (SD) for continuous variables and N (%) for categorical variables.

demographics of the study participants. When compared to the controls, illicit drug users were more likely to be smokers, drinkers, and physically inactive. Illicit drug users also had lower BMD at the femoral neck, as well as lower ACT and BMD at the narrow neck. The number of illicit drug users with prior use of antipsychotics or antidepressants was higher than the controls, both within 1 year and 5 years before skeletal health assessment.

3.2. Association of illicit drug use with BMD

Table 3 shows the association result of illicit drug use with BMD. When compared to non-drug users, illicit drug use was significantly associated with lower BMD at the femoral neck in Model 1 (adjusted for age and BMI). After further adjustments in Models 2 and 3, illicit drug use was significantly associated with reduced BMD at both skeletal sites, with an estimated mean difference of −0.062 g/cm^2 (95% CI, −0.108 to −0.015) and −0.058 g/cm^2 (95% CI, −0.106 to −0.010) observed for BMD at the lumbar spine and femoral neck respectively in the fully adjusted model. Results of the subgroup analysis by individual drug category are provided in Table 3. Similar reductions in BMD were observed in the sensitivity analysis (Supplementary Table S1).

3.3. Association of illicit drug use with hip geometric parameters

The results of the association between illicit drug use and hip geometric parameters at the narrow neck are shown in Table 4. In Model 1, illicit drug use was significantly associated with reduced CSA, ACT, and BMD of the narrow neck when compared to non-users. After further adjustment in Model 2, all 5 narrow neck parameters were reduced in illicit drug users compared to non-users. However, in Model 3, which was further adjusted for antipsychotic and antidepressant use, illicit drug use was significantly associated only with reductions in CSA, ACT, and BMD with a mean difference of −0.238 cm^2 (95% CI: −0.462 to −0.013), −0.018 cm (95% CI, −0.030 to −0.006) and −0.070 g/cm^2 (95% CI, −0.128 to −0.012) respectively. Results of the subgroup analysis of each drug category are provided in Table 4. In the sensitivity analysis (Supplementary Table S2), similar results were observed, except that the association of illicit drug use and CSA became marginally significant (FDR = 0.051), the association of users of the “others” drug category with CSA became insignificant and the association between opioid users and CSMI became significant.

4. Discussion

In this study, we showed a significant reduction in BMD as well as hip geometric parameters at the narrow neck in illicit drug users when compared to non-users. To the best of our knowledge, this is one of the largest and most comprehensive studies investigating the relationship of illicit drug use with bone health. No studies have investigated the relationship of illicit drug use with hip geometry at the narrow neck previously. Reduction of BMD among illicit drug users was approximately −0.39SD (−0.062 g/cm^2) and −0.45SD (−0.058 g/cm^2) at the lumbar spine and femoral neck respectively, when compared to non-users. Furthermore, illicit drug users also had reduced hip geometric parameters, which were approximately −0.42SD (−0.238 cm^2), −0.54SD (−0.018 cm), and −0.44SD (−0.070 g/cm^2) for CSA, ACT, and BMD at the narrow neck, respectively.

4.1. Association of individual drug categories with BMD

The subgroup analyses by individual drug category of opioids (N = 57) and stimulants (N = 22) were consistent with previous studies. Previous studies demonstrated associations of opioid use with lower BMD in men [7,10,22] and women [8,23–25]. Furthermore, an earlier study found that lumbar spine BMD was lower in 46 male methamphetamine abusers than 188 controls [9]. On the other hand, the use of cannabis (N = 8) was not significantly associated with a reduction in BMD in the current study, while a previous study showed a significant reduction in BMD at three skeletal sites in heavy cannabis users compared to cigarette smokers [6]. This difference in results may be attributed to the study design, as the previous study used smokers as the control group, or the low sample size of this drug category in the current study. Our study also reported the association of hallucinogen (N = 5) use with BMD for the first time. The hallucinogen group consisted of

Table 3
Association of illicit drug use with bone mineral density. Subgroup analysis by drug category was done using the fully adjusted model (model 3).

Parameter	Class	Difference	S.E.	Lower	Upper	P-value	FDR
Lumbar Spine	All drugs-model 1	−0.032	0.019	−0.069	0.006	0.100	0.110
	All drugs-model 2	−0.066	0.024	−0.113	−0.020	0.005	0.022
	All drugs-model 3	−0.062	0.024	−0.108	−0.015	0.009	0.022
	Cannabis	−0.049	0.036	−0.120	0.022	0.174	–
	Hallucinogens	−0.037	0.055	−0.144	0.071	0.503	–
	Opioids	−0.068	0.030	−0.126	−0.010	0.023	–
	Others	−0.012	0.035	−0.081	0.057	0.724	–
	Stimulants	−0.087	0.030	−0.146	−0.029	0.003	–
Femoral Neck	All drugs-model 1	−0.043	0.017	−0.077	−0.010	0.011	0.022
	All drugs-model 2	−0.064	0.024	−0.112	−0.016	0.009	0.022
	All drugs-model 3	−0.058	0.024	−0.106	−0.010	0.019	0.028
	Cannabis	−0.036	0.037	−0.110	0.038	0.334	–
	Hallucinogens	−0.109	0.050	−0.208	−0.010	0.030	–
	Opioids	−0.049	0.027	−0.103	0.005	0.077	–
	Others	−0.054	0.032	−0.117	0.010	0.098	–
	Stimulants	−0.074	0.026	−0.125	−0.022	0.005	–

Model 1 – Adjusted for age and BMI. Model 2 – Adjusted for age, BMI, physical activity, status of drinking and status of smoking. Model 3 – Adjusted for age, BMI, physical activity, status of drinking, status of smoking, use of antidepressants and antipsychotics.

Table 4
Association of illicit drug users with hip geometric parameters at the narrow neck. Subgroup analysis by drug category was done using the fully adjusted model (model 3).

Parameter	Class	Difference	S.E.	Lower	Upper	P-value	FDR
Cross sectional area	All drugs-model 1	−0.183	0.071	−0.324	−0.043	0.011	0.022
	All drugs-model 2	−0.296	0.112	−0.517	−0.076	0.009	0.022
	All drugs-model 3	−0.238	0.114	−0.462	−0.013	0.038	0.050
	Cannabis	−0.076	0.198	−0.467	0.314	0.701	–
	Hallucinogens	−0.407	0.267	−0.933	0.120	0.129	–
	Opioids	−0.262	0.123	−0.505	−0.020	0.034	–
	Others	−0.305	0.151	−0.603	−0.008	0.044	–
	Stimulants	−0.207	0.127	−0.456	0.043	0.105	–
Cross-sectional moment of inertia	All drugs-model 1	−0.190	0.117	−0.421	0.041	0.106	0.112
	All drugs-model 2	−0.421	0.192	−0.801	−0.042	0.030	0.042
	All drugs-model 3	−0.298	0.201	−0.694	0.099	0.140	0.140
	Cannabis	−0.084	0.311	−0.697	0.528	0.786	–
	Hallucinogens	−0.248	0.511	−1.255	0.760	0.628	–
	Opioids	−0.483	0.247	−0.971	0.005	0.053	–
	Others	−0.361	0.311	−0.975	0.253	0.248	–
	Stimulants	−0.095	0.243	−0.574	0.385	0.698	–
Section Modulus	All drugs-model 1	−0.086	0.047	−0.179	0.006	0.066	0.079
	All drugs-model 2	−0.183	0.073	−0.326	−0.040	0.012	0.022
	All drugs-model 3	−0.139	0.076	−0.289	0.010	0.067	0.079
	Cannabis	−0.046	0.135	−0.313	0.221	0.733	–
	Hallucinogens	−0.186	0.199	−0.578	0.206	0.350	–
	Opioids	−0.171	0.088	−0.345	0.003	0.054	–
	Others	−0.168	0.115	−0.395	0.059	0.145	–
	Stimulants	−0.109	0.089	−0.285	0.067	0.223	–
Average cortical thickness	All drugs-model 1	−0.015	0.004	−0.024	−0.007	0.001	0.013
	All drugs-model 2	−0.019	0.006	−0.031	−0.007	0.002	0.019
	All drugs-model 3	−0.018	0.006	−0.030	−0.006	0.004	0.022
	Cannabis	−0.013	0.010	−0.033	0.007	0.188	–
	Hallucinogens	−0.035	0.013	−0.060	−0.010	0.006	–
	Opioids	−0.013	0.007	−0.027	0.001	0.066	–
	Others	−0.019	0.008	−0.034	−0.003	0.019	–
	Stimulants	−0.023	0.007	−0.036	−0.010	< 0.001	–
BMD	All drugs-model 1	−0.054	0.021	−0.096	−0.012	0.011	0.022
	All drugs-model 2	−0.077	0.029	−0.135	−0.020	0.009	0.022
	All drugs-model 3	−0.070	0.029	−0.128	−0.012	0.019	0.028
	Cannabis	−0.042	0.049	−0.137	0.054	0.390	–
	Hallucinogens	−0.153	0.061	−0.273	−0.033	0.013	–
	Opioids	−0.049	0.034	−0.116	0.018	0.148	–
	Others	−0.073	0.039	−0.149	0.003	0.059	–
	Stimulants	−0.096	0.031	−0.157	−0.034	0.002	–

Model 1 – Adjusted for age and BMI. Model 2 – Adjusted for age, BMI, physical activity, status of drinking and status of smoking. Model 3 – Adjusted for age, BMI, physical activity, status of drinking, status of smoking, use of antidepressants and antipsychotics.

ketamine users and hallucinogen use was associated with reduced BMD at the femoral neck. Previously, a study conducted in 28 patients with treatment-resistant major depressive disorder suggested both a negative and positive effect of acute ketamine treatment on BMD [26]. It's important to note that the sample size for this group was limited, and cautious interpretation is required. Due to the small sample size of the sedatives, hypnotics, or anxiolytics (SHA) (N = 2) drug category, this group was excluded from the subgroup analysis and is instead presented in the supplementary material (Supplementary Table S3). Due to the small sample size, it is impossible that the SHA users in the community were adequately represented, and a valid conclusion could not be drawn. The SHA group consisted of midazolam users, and we observed a reduction in BMD at the lumbar spine and femoral neck. No prior study has been conducted to investigate this relationship in humans, but an in vitro study found that midazolam suppresses osteogenesis in mesenchymal stem cells [27], suggesting an adverse effect on BMD. Further research into the effects of SHA and hallucinogen use on BMD is warranted.

4.2. Illicit drug use and hip geometry

In this study, we further demonstrated that illicit drug use was associated with poor hip geometry. In this study, we analyzed the narrow neck in this analysis as this region of the femoral neck is routinely measured as part of hip structural analysis programs and is a common site where hip fractures occur [15,16,28–31]. CSA, CSMI, and SM of the narrow neck estimated by hip structure analysis were shown to be highly correlated with those corresponding parameters measured by QCT, with $r \geq 0.93$ [15]. A previous study showed that reductions in all five parameters used in the current study were associated with increased hip fracture [16]. Among these, reduced BMD and ACT were shown to be particularly strong predictors of incident hip fracture. In the current study, we observed a significant reduction of CSA, ACT and BMD at the narrow neck in illicit drug users vs non-users. In the sensitivity analysis, the association between illicit drug use and CSA was marginally significant after correction for multiple testing (FDR = 0.051), however, multiple testing corrections may be overly conservative when the traits are correlated. Therefore, cautious interpretation is required. Reductions were also observed for CSMI and SM, although these were statistically insignificant. Opioid use was associated with reduced CSA. Furthermore, hallucinogen, and stimulant use were associated with reduced ACT and BMD at the narrow neck. SHA users had reduced CSA, ACT and BMD at the narrow neck (Supplementary Table S3), warranting further research.

Bone strength can be assessed through two primary mechanisms: resistance against compression and tension, and resistance against bending and torsion forces. Metrics related to bone mineral content within a cross-sectional area, such as BMD, CSA, and ACT, reflect bone strength against compression and tension. Conversely, metrics involving the distribution of bone mineral around the central axis, such as CSMI and SM, offer insights into bone strength against bending and torsional forces [32,33]. The findings of this study suggest a connection between illicit drug usage and diminished CSA, ACT, and BMD at the narrow neck. However, no statistically significant changes were observed in CSMI and SM at this site. This suggests that in illicit drug users, the bone at the narrow neck region has a reduced capacity to resist compressive and tensile stresses, but no significant difference in the capacity to resist bending and torsional stresses. Thus, our study shows that illicit drug use could lead to reduced bone mass and deterioration of bone structure, thereby increasing the risk of fragility fracture. Future studies evaluating the fracture risk among illicit drug users are warranted.

4.3. Clinical implications

Our study has important clinical implications. Illicit drug use on bone health has been rarely investigated and it remains unclear whether or not illicit drug use is associated with adverse bone health. In our current study, we showed that illicit drug users had a lower BMD at all sites measured, as well as a deterioration in hip geometric parameters at the narrow neck. Furthermore, the observed reductions were substantial, with statistically significant reductions of approximately −0.39SD and −0.45SD at the lumbar spine, and femoral neck respectively. In addition, illicit drug users also had reduced hip geometric parameters at the narrow neck, which were −0.42SD, −0.54SD, and −0.44SD for CSA, ACT, and BMD, respectively. Although impaired bone health could be asymptomatic, it is known to be associated with an increased risk of fragility fracture. Therefore, the results put forward in this study should be communicated to the population, especially among illicit drug users. Furthermore, while our study provides robust evidence that illicit drug use is associated with poor bone health, our study also presents an important message to healthcare professionals: healthcare professionals should evaluate the bone health among illicit drug users, and timely clinical management should be arranged to reduce subsequent risk of fracture. This is particularly important as bone health is commonly neglected as a complication of illicit drug use.

4.4. Strengths and limitations

There are several strengths in the current study. Due to the significantly different age and sex distribution between participants with illicit drug use and controls without illicit drug use from the HKOS cohort, controls were age- and sex-matched to drug users. We adjusted for the use of antidepressants and antipsychotics which has not been done in previous studies. Since antidepressant and antipsychotics were also associated with poor bone health [34,35], which could confound the association. Therefore, it is important for future studies to take these covariates into consideration. The history of illicit drug use was assessed by experienced pharmacists in a thorough in-person interview, enabling the collection of detailed information. We investigated the association of illicit drug use with hip geometric parameters for the first time. There are also limitations. First, like all other studies related to illicit drug use, the biggest challenges include recall bias and the evaluation of independent drug effects. The most used illicit drug was self-reported, which is subjected to recall bias. Given that most illicit drug users use more than just one illicit drug, it is impossible to separate the independent effect of each illicit drug on bone health and it is possible that the most used illicit drug for each individual was not consistent over their lifetime. Second, the number of participants in each illicit drug group was small, thus null associations could be due to insufficient power. Due to these two limitations, the results of the subgroup analysis, especially for those groups with a small sample size, should be interpreted cautiously. Third, the number of female drug users was small, thereby disallowing sex-specific analysis due to limited power. Fourth, blood biomarkers, which could provide important information regarding differences in bone formation and resorption due to illicit drug use, and drug use duration and intensity were not evaluated in this study. Further studies incorporating blood-based biomarkers, drug dose, and length of drug use may provide further insight into the relationship between drug use and adverse outcomes. Fifth, no causality can be inferred as this study is cross-sectional in nature. Sixth, residual confounding is possible.

5. Conclusions

In the current study, illicit drug users had a lower BMD and deterioration in hip geometric parameters at the narrow neck when compared with non-users. This finding should be disseminated to improve the awareness of the adverse effects of illicit drug use on bone health, while clinical management of bone health in illicit drug users may help to reduce future risk of fragility fracture.

CRediT author statement

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Conflicts of interest

The auhors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2023.09.001.

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