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Abstract

The relationship of illicit drug use with musculoskeletal health is largely unknown. In this study, we evaluated the association of illicit drug use with bone mineral density (BMD) and muscle parameters in 108 illicit drug users (including current users and those with history of illicit drug use) and 1345 non-users from the Chinese population residing in Hong Kong. BMD was measured using dual energy X-ray absorptiometry (DXA). Skeletal muscle mass, function and strength as represented by appendicular lean mass (ALM), gait speed and handgrip strength were assessed by bioimpedance analyzer, 6-meter walk test and dynamometer, respectively. Peak expiratory flow (PEF) rate, a measure of function and strength of the respiratory muscle, was also tested by a hand-held peak flow meter. Analysis of covariance (ANCOVA) was applied to evaluate the association of illicit drug use with various bone and muscle parameters, with adjustment for age, sex, body mass index, smoking and drinking status, and physical activity. Compared with non-users, individuals with illicit drug use had a lower BMD (g/cm^2) at lumbar spine (mean difference: -0.046), femoral neck (-0.047), and total hip (-0.05). Similarly, illicit drug use was significantly associated with reduced muscle parameters when compared to the non-users, with the estimated mean difference of -0.656kg, -0.107m/s, -1.852kg, and 59.24 L/min for ALM, gait speed, grip strength, and PEF rate, respectively. In conclusion, individuals with illicit drug use were shown to have reduced BMD, diminished skeletal and respiratory muscle health when compared to non-users, implying that illicit drug users may have elevated risk of morbidity (such as osteoporosis and sarcopenia), decreased quality of life, increased risk of immobility and mortality. Such findings should be disseminated to the public for motivating the quitting intention of drug abusers and reducing illicit drug use. It may also provide the basis for the healthcare professionals to formulate plans to improve the musculoskeletal health of illicit drug users.

研究摘要

由於吸毒與肌肉骨骼健康之間的關係仍未清晰，本研究招募於香港居住的中國籍人士作研究對象，當中包括 108 名吸毒者 (包括正在吸毒和已戒毒人士) 及 1345 名非吸毒者，旨在評估吸毒與骨質密度和肌肉參數之間的關係。

研究人員透過雙能量 X 光為研究對象進行骨質密度檢查，並通過生物電阻分析儀量度四肢骨骼肌肉質量、6 米步速和手握力測試以分別評估骨骼肌的功能和強度，研究對象還須接受峰值呼氣流量測試，以評估呼吸肌的功能和強度。在量度以上數據後，是次研究利用共變數分析 (ANCOVA)方法，在控制年齡、性別、體重指數、吸煙、飲酒及運動狀況下，比較吸毒者與非吸毒者的各種骨骼和肌肉參數，從而計算出吸毒與骨骼肌肉健康的關聯。

與非吸毒者相比，吸毒者於腰椎（平均差異：-0.046），股骨頸（-0.047）和全髖關節（-0.05）的骨質密度（g / cm2）均較非吸毒者低。同樣地，吸毒者的肌肉參數也較非吸毒者為低，他們的四肢骨骼肌肉質量、步速、手握力及峰值呼氣流量的平均差異分別為-0.656kg，-0.107m / s，-1.852kg 和 59.24 L / min。

綜上所述，吸毒者的骨質密度、骨骼和呼吸肌肉的參數與非吸毒者相比顯著偏低，意味著他們有更高風險患上其他相關疾病(如骨質疏鬆症及肌肉減少症)，生活質素下降，行動不便，甚至死亡。是項研究結果或會有助鼓勵吸毒者戒毒及減少吸毒的次數，以及為醫護人士對吸毒者制定針對肌肉骨骼健康的計劃提供基礎。

Declaration

This research project has been completed by the research team at the Department of Pharmacology and Pharmacy, the Li Ka Shing Faculty of Medicine, the University of Hong Kong.

Ethics approval has been obtained from 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).

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Chapter 1. Introduction

Illicit drug use is known to be significantly associated with personal, societal, and public health consequences. Although the overall trend of reported illicit drug use has been decreasing steadily in Hong Kong, illicit drug use could still lead to adverse health outcomes, such as psychiatric disorders, cardiovascular diseases, and impaired cognitive function. However, the relationship of illicit drug use with other body systems is less understood, especially musculoskeletal system.

Among the commonly used illicit drugs, use of heroin (1, 2), methadone (3, 4), diacetylmorphine (5), and methylamphetamine (6) were reported to be associated with reduced bone mineral density (BMD). Conversely, to the best of our knowledge, no research studies have been conducted to investigate the relationship of illicit drug use with muscle health. Since patients with osteoporotic fracture and sarcopenia are not only associated with increased risk of morbidity and mortality, but also increased risk of dependency, immobility, and institutionalization, musculoskeletal health is a social issue instead of merely a healthcare issue. Understanding the relationship of illicit drug use with musculoskeletal health is clinically important. In particular, such data is unavailable in Hong Kong or even in any Chinese population, while it has been well-documented that musculoskeletal traits are largely affected by ethnicities. In the current study, we aimed to evaluate the association of illicit drug use with BMD and muscle health among 108 illicit drug users and 1345 non-users from the Chinese population residing in Hong Kong.

Chapter 2. Materials and methods

2.1 Participants

In this study, illicit drug users were defined as current illicit drug users, and those with history of illicit drug use. Illicit drug users (N=108) were recruited via referral from local drug treatment and social rehabilitation service centres, and substance abuse clinic in the Hong Kong West Cluster. Among the 1391 participants from the in-person follow up study of the Hong Kong Osteoporosis Study (HKOS) (7), those with missing data were excluded [smoking status (N=4), drinking status (N=13), physical activity (N=1), BMI (N=3), BMD (N=6), lean mass (N=20), gait speed (N=8), handgrip strength (N=2), and peak expiratory flow rate (PEF, N=5); with a number of participants having multiple missing data]. A total of 1345 participants were used as the controls in the final analysis. All participants were of Chinese ethnicity. They were assessed by a trained research assistant or nurse for physical measurement. Their basic demographic information and lifestyle factors were collected using a structured questionnaire. For illicit drug users, detailed medication and drug abuse history was recorded by a trained registered pharmacist. They were grouped into one single drug use category based on the highest frequency of use before their medication review with the pharmacist. Multi-drug users were not considered as one category in the current study, due to the relatively small sample size for various combinations of drug use. The study has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All participants gave informed consent for participating in the study.

2.2 Musculoskeletal health assessments

BMD was measured using a Hologic Discovery A dual energy X-ray absorptiometry (DXA) (Waltham, MA, USA). All DXA measurements were performed by trained technicians using a

standardized protocol of measurement. Daily quality control scans were performed using the spine phantom and across the DXA machine to ensure consistent measurement. Appendicular lean mass (ALM) was measured using a bioimpedance analyzer (Tanita MC780-MA, Tanita Corp, Tokyo, Japan). Handgrip strength was measured for the dominant hand using a dynamometer. Peak expiratory flow (PEF) rate was measured with a hand-held peak flow meter. Both the handgrip strength and PEF rate were measured for 3 times, with at least 5 minutes apart for each measurement, and the average value was used for subsequent analysis. Gait speed was measured in a 6-meter walk test. Serum calcium, phosphate, and creatinine levels were measured using Ortho-Vitros Fusion 5.1 (Johnson & Johnson). According to the World Health Organization, osteoporosis was defined as BMD T-score ≤ -2.5 at either lumbar spine or hip, while osteopenia was defined as BMD T-score of >-2.5 and ≤ -1. Sarcopenia was defined based on the 2019 consensus update of the Asian Working Group for Sarcopenia: (i) low muscle mass defined as height-adjusted appendicular skeletal muscle mass of <7kg/m^2 in men and <5.4 kg/m^2 in women as measured by DXA; or <7.0 kg/m^2 in men and <5.7 kg/m^2 in women as measured by bioimpedance; (ii) low muscle strength defined as handgrip strength <28kg for men and <18kg for women; (iii) low physical performance defined as 6-meter walk <1.0m/s, short physical performance battery score ≤9, or 5-time chair stand test ≥12 seconds. Individuals with low muscle mass plus low muscle strength and / or low physical performance were considered having sarcopenia (8).

2.3 Covariates

Basic demographic information, drinking and smoking status of each study participant was obtained from a structured questionnaire. Their smoking and drinking status were categorized into current-, ex-, and never- smoker or drinker. Their physical activity was evaluated using

the modified Yale Physical Activity Survey (YPAS) questionnaire (9), which was previously validated in Chinese (10). The intensity of each type of physical activity was expressed as a corresponding metabolic equivalent (MET), defined as the energy expenditure at resting metabolic rate(11).

The physically active group (11) is defined as individuals who had:

- physical activity with MET greater than 6 (i.e. vigorous), the number of sessions per week must be at least 3, and the total time spent per week must be at least 180 minutes.
- physical activity with MET between 3 and 6 (i.e. moderate), the number of sessions per week must be at least 5, and the total time spent per week must be at least 300 minutes.

Physically inactive group was defined as those with no self-reported leisure time physical activity. Minimally active group was defined as those who did not fall into the physically inactive group, but their amount of physical activity did not fulfil the definition of being physically active, including those who had physical activity with MET of less than 3, but the time spent on these activities would not be counted towards being physical active.

2.4 Statistical Analysis

For descriptive statistics, the demographic characteristics are expressed as mean ± standard deviation (SD) for continuous variables or frequencies for categorical variables. The differences between drug abusers and controls were compared by t-test and chi-square test for continuous and categorical variable, respectively. Analysis of covariance (ANCOVA) was used to evaluate the association of drug abuse with various clinical outcomes, with adjustment

for age, sex, and body mass index (BMI) in model 1; further adjustment for physical activity, smoking and drinking status in model 2. Analyses investigating the association of each individual illicit drug group with different clinical outcomes were also conducted. Due to the limited number of female participants in the current study, subgroup analysis by sex was not conducted. All analyses were done using IBM SPSS Statistics for Windows, Version 26.0. (Armonk, NY: IBM Corp).

Chapter 3. Results

3.1 Demographics of the illicit drug users

Table 1 shows the illicit drugs used by the drug users. Heroin was the most frequently used illicit drugs (N=53, 49.1%), followed by methamphetamine (N=19, 17.6%) and cannabis (N=8, 7.4%). Demographic information of both the illicit drug users and controls are shown in Table 2. When compared with the non-drug users, illicit drug users were younger and more often male, drinker, smoker, and physically inactive. Age, sex, drinking status, smoking status and physical activity are known to affect both bone and muscle parameters, so they were adjusted as covariates in subsequent ANCOVA analyses (Chapter 3.2-3.4). Without taking into account these covariates, t-test demonstrated that the illicit drug users had higher serum creatinine, BMD at all sites measured, ALM, handgrip strength, and PEF, but lower serum calcium and phosphorus levels, when compared to the non-users.

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

Category	Drug	Count	Percentage
Hallucinogens	Cannabis / Marijuana	8	7.4
Depressants	Amyl nitrite	1	0.9
Depressants	Gamma Hydroxybutyric Acid	1	0.9
Narcotics Analgesics	Heroin	53	49.1
Narcotics Analgesics	Methadone	3	2.8
Narcotics Analgesics	Opiates / Opium	1	0.9
Tranquillizers	Midazolam	2	1.9
Stimulants	Cocaine	1	0.9
Stimulants	Methamphetamine	19	17.6
Stimulants	Methylenedioxymethamphetamine	2	1.9
Others	Ketamine	5	4.6
Others	Others	4	3.7
Others	Unknown	8	7.4

Table 2. Demographic information of the study participants (N=1453).

	Control (N=1345)			Illicit drug users (N=108)			P
Age (years)	57.99	±	11.85	49.67	±	14.28	<0.001
Female (%)	1063		(79.0)	14		(13.0)	<0.001
BMI	23.28	±	3.64	23.73	±	4.17	0.218
Smoking status (%)							<0.001
non-smoker	1265		(94.1)	17		(15.7)	
ex-smoker	48		(3.6)	16		(14.8)	
current-smoker	32		(2.4)	75		(69.4)	
Drinking status (%)							<0.001
non-drinker	881		(65.5)	21		(19.4)	
ex-drinker	141		(10.5)	35		(32.4)	
current-drinker	323		(24.0)	52		(48.1)	
Physical activity (%)							0.002
Inactive	308		(22.9)	40		(37.0)	
Active	203		(15.1)	8		(7.4)	
Minimally active	834		(62.0)	60		(55.6)	
Creatinine (umol/L)*	67.37	±	29.23	77.56	±	15.05	0.001
Serum calcium (mmol/L)*	2.328	±	0.095	2.302	±	0.099	0.01
Serum phosphorus (mmol/L)*	1.242	±	0.160	1.111	±	0.202	<0.001
BMD (g/cm2) at							
Lumbar spine (L1-L4)	0.924	±	0.167	0.977	±	0.145	<0.001
Femoral neck	0.703	±	0.127	0.753	±	0.105	<0.001
Total hip	0.830	±	0.132	0.888	±	0.119	<0.001
BMD T-score at							
Lumbar spine (L1-L4)	-0.60	±	1.33	-0.12	±	1.15	<0.001
Femoral neck	-0.41	±	1.16	-0.28	±	0.98	0.249
Total hip	-0.83	±	1.12	-0.50	±	0.78	0.003
Appendicular lean mass (kg)	15.11	±	3.59	19.75	±	3.89	<0.001
Gait speed (m/s)	1.21	±	0.23	1.21	±	0.28	0.915
Handgrip strength (kg)	23.84	±	7.84	33.62	±	8.25	<0.001
Peak expiratory flow (liters per minute)	318.4	±	96.6	358.6	±	114.2	<0.001
Osteoporosis	128		(9.5)	1		(0.9)	0.004
Osteopenia	727		(54.1)	42		(38.9)	0.003
Fracture	117		(8.7)	3		(2.8)	0.049
Sarcopenia	258		(19.2)	20		(18.5)	0.967

The demographic characteristics are expressed as mean ± standard deviation for continuous variables, or number (percentage) for categorical variables.

*data were available in 1190 controls and 108 illicit drug users.

3.2 Prevalence of osteoporosis, osteopenia, fracture and sarcopenia in illicit drug users

The number of illicit drug users who met the definition of osteoporosis, osteopenia and sarcopenia at assessment were listed out in Table 2. The number of illicit drug users who had prior history of fracture were also recorded in Table 2. Out of the 108 illicit drug users included in this study, the prevalence of osteoporosis, osteopenia, sarcopenia and fracture were 0.9%, 38.9.9%, 18.55% and 2.8%, respectively. Although the figures in Table 2 seem to show a higher prevalence of osteoporosis, osteopenia, sarcopenia and fracture among the non-drug users, they are known to be more prevalent with increased age and they were influenced by other factors, such as sex, physical activity, etc. While the illicit drug users included in our study were relatively young and predominantly male, the non-drug users were older and mostly female. We therefore evaluated the prevalence of osteoporosis, osteopenia, sarcopenia and fracture among male study participants aged ≥60 only (Table 3). Out of the 33 illicit drug users aged ≥60, the prevalence of osteoporosis, osteopenia, sarcopenia and fracture were 3%, 48.5%, 27.3% and 0% respectively. There was no significant difference between the prevalence in the illicit drug users and the non-drug users in this subgroup.

Table 3. Number of study participants with osteoporosis, osteopenia, sarcopenia and fracture in male study participants aged ≥60

	Control (N=150)	Illicit drug users (N=33)	P
Age (years)	69.01 ± 6.12	65.82 ± 3.14	0.004
Osteoporosis	3 (2.0)	1 (3.0)	1.000
Osteopenia	68 (45.3)	16 (48.5)	0.892
Fracture	11 (7.3)	0 (0)	0.230
Sarcopenia	41 (27.3)	9 27.3	1.000

The demographic characteristics are expressed as mean ± standard deviation for continuous variables, or number (percentage) for categorical variables.

3.3 Association of illicit drug use with BMD

Table 4 shows the association result of illicit drug use with BMD. In model 1 adjusted for age, sex, and BMI, illicit drug use was significantly associated with lower BMD at the lumbar spine, femoral neck, and total hip (all $P<0.05$), when compared with non-drug users. Similar findings were observed after further adjustment for smoking status, drinking status, and physical activity in model 2, with the estimated mean difference of -0.046g/cm^2, -0.047 g/cm^2 and -0.05 g/cm^2 for BMD at lumbar spine, femoral neck, and total hip, respectively. We also examined the association of individual illicit drug group with BMD (Table 5). Use of tranquilizers was significantly associated with reduced BMD at the femoral neck and total hip (Tables 5b and 5c), while use of stimulants was significantly associated with reduced BMD at all sites measured (Tables 5a-c).

Table 4. Association of illicit drug use with bone mineral density.

	Model 1				Model 2			
	Mean difference	95% CI		P	Mean difference	95% CI		P
		lower	upper			lower	upper	
BMD (g/cm2) at								
Lumbar spine	-0.037	-0.070	-0.005	0.023	-0.046	-0.089	-0.004	0.033
Femoral neck	-0.041	-0.064	-0.018	<0.001	-0.047	-0.078	-0.017	0.002
Total hip	-0.045	-0.069	-0.022	<0.001	-0.05	-0.081	-0.019	0.001

Model 1: Adjusted for age, sex, and BMI

Model 2: Model 1 and further adjusted for smoking status, drinking status, and physical activity.

Table 5. Association of different illicit drug users with BMD at (a) lumbar spine, (b) femoral neck, and (c) total hip

(a) BMD at the lumbar spine

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	0.939		Ref		
Hallucinogens	0.87	-0.069	-0.176	0.038	0.206
Depressants	0.872	-0.066	-0.273	0.141	0.529
Narcotics Analgesics	0.935	-0.004	-0.057	0.049	0.884
Tranquillizers	0.749	-0.190	-0.399	0.020	0.076
Stimulants	0.822	-0.116	-0.185	-0.048	<0.001
Others or unknown	0.908	-0.030	-0.109	0.049	0.452

(b) BMD at the femoral neck

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	0.712		Ref		
Hallucinogens	0.661	-0.051	-0.127	0.025	0.187
Depressants	0.674	-0.038	-0.185	0.109	0.611
Narcotics Analgesics	0.695	-0.017	-0.055	0.021	0.375
Tranquillizers	0.545	-0.167	-0.316	-0.019	0.027
Stimulants	0.624	-0.088	-0.136	-0.040	<0.001
Others or unknown	0.648	-0.064	-0.120	-0.008	0.025

(c) BMD at the total hip

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	0.841		Ref		
Hallucinogens	0.792	-0.050	-0.126	0.027	0.207
Depressants	0.805	-0.037	-0.186	0.112	0.629
Narcotics Analgesics	0.826	-0.015	-0.053	0.023	0.436
Tranquillizers	0.676	-0.165	-0.316	-0.014	0.032
Stimulants	0.746	-0.096	-0.145	-0.046	<0.001
Others or unknown	0.765	-0.077	-0.133	-0.020	0.008

The analysis was adjusted for age, sex, BMI, physical activity, and smoking and drinking status.

3.4 Association of illicit drug use with muscle parameters

Table 6 shows the association result of illicit drug use with muscle parameters. In model 1 adjusted for age, sex, and BMI, illicit drug use was significantly associated with lower ALM, gait speed, and PEF (all $P<0.05$). The association with handgrip strength was not statistically significant. However, after further adjustment for smoking status, drinking status and physical activity in model 2, the association with handgrip strength became statistically significant. The estimated mean difference was -0.656kg, -0.107m/s, -1.852kg, and 59.24 L/min for ALM, gait speed, handgrip strength, and PEF, respectively, when compared with non-drug users. When the subgroup analysis was conducted for individual illicit drug group and muscle parameters (Table 7), use of hallucinogens was significantly associated with reduced ALM, handgrip strength, and PEF (Tables 7a, 7c, and 7d). Depressant use was significantly associated with reduced handgrip strength (Table 7c). Use of narcotics Analgesics was significantly associated with reduced ALM and PEF (Tables 7a and 7d). Stimulant use was significantly associated with reduced gait speed, handgrip strength, and PEF (Tables 7b, 7c, and 7d).

Table 6. Association of illicit drug use with muscle parameters.

	Model 1				Model 2			
	Mean difference	95% CI		P	Mean difference	95% CI		P
		lower	upper			lower	upper	
ALM (kg)	-0.424	-0.817	-0.032	0.034	-0.656	-1.172	-0.139	0.013
Gait speed (m/s)	-0.094	-0.139	-0.049	<0.001	-0.107	-0.166	-0.047	<0.001
Handgrip strength (kg)	-0.438	-1.638	0.763	0.475	-1.852	-3.428	-0.276	0.021
PEF (liters per minute)	-82.91	-98.26	-67.56	<0.001	-59.24	-79.38	-39.09	<0.001

Model 1: Adjusted for age, sex, and BMI

Model 2: Model 1 and further adjusted for smoking status, drinking status, and physical activity.

Table 7. Association of different illicit drug users with (a) ALM, (b) gait speed, (c) handgrip strength, and (d) PEF

(a) ALM

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	15.70		Ref		
Hallucinogens	13.19	-2.51	-3.81	-1.22	<0.001
Depressants	15.92	0.21	-2.29	2.71	0.868
Narcotics Analgesics	14.90	-0.80	-1.44	-0.16	0.015
Tranquillizers	17.06	1.36	-1.17	3.89	0.292
Stimulants	15.84	0.14	-0.69	0.96	0.748
Others or unknown	14.83	-0.87	-1.83	0.08	0.073

(b) gait speed

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	1.236		Ref		
Hallucinogens	1.186	-0.050	-0.200	0.099	0.507
Depressants	1.010	-0.226	-0.515	0.063	0.126
Narcotics Analgesics	1.171	-0.065	-0.139	0.009	0.083
Tranquillizers	1.396	0.160	-0.133	0.452	0.284
Stimulants	1.033	-0.203	-0.299	-0.108	<0.001
Others or unknown	1.136	-0.100	-0.210	0.010	0.074

(c) handgrip strength

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	25.07		Ref		
Hallucinogens	19.52	-5.55	-9.46	-1.64	0.005
Depressants	14.68	-10.40	-17.97	-2.82	0.007
Narcotics Analgesics	26.84	1.77	-0.17	3.70	0.074
Tranquillizers	27.25	2.18	-5.49	9.85	0.577
Stimulants	19.64	-5.44	-7.93	-2.94	<0.001
Others or unknown	21.63	-3.44	-6.33	-0.56	0.019

(d) PEF

Drug user categories	Estimated Mean	Estimated mean difference	95% CI		P
			Lower	upper	
Non-users	314.2		Ref		
Hallucinogens	237.0	-77.2	-127.8	-26.6	0.003
Depressants	305.0	-9.2	-107.2	88.8	0.854
Narcotics Analgesics	259.9	-54.3	-79.4	-29.2	<0.001
Tranquillizers	335.1	20.9	-78.3	120.0	0.680
Stimulants	241.4	-72.8	-105.2	-40.5	<0.001
Others or unknown	253.8	-60.5	-97.8	-23.1	0.002

The analysis was adjusted for age, sex, BMI, physical activity, and smoking and drinking status.

3.5 Association of illicit drug use with serum bone and kidney biomarkers

Table 8 shows the association result of illicit drug use with serum bone and kidney biomarkers. Illicit drug use was significantly associated with reduced serum phosphorus in model 1 (adjusted for age, sex, and BMI), but the association became statistically insignificant after further adjustment for physical activity and smoking and drinking status in model 2.

Table 8. Association of illicit drug use with serum bone and kidney biomarkers.

	Model 1				Model 2			
	Mean difference	95% CI		P	Mean difference	95% CI		P
		lower	upper			lower	upper	
Creatinine (umol/L)	-0.580	-6.624	5.465	0.851	-0.657	-8.662	7.349	0.872
Serum calcium (mmol/L)	-0.021	-0.042	0.000	0.053	-0.006	-0.034	0.022	0.676
Serum phosphorus (mmol/L)	-0.035	-0.069	-0.001	0.046	-0.040	-0.086	0.005	0.084

Model 1: Adjusted for age, sex, and BMI

Model 2: Model 1 and further adjusted for smoking status, drinking status, and physical activity.

Chapter 4. Discussion

4.1 Illicit drug use and musculoskeletal health

To the best of our knowledge, this is the largest and most comprehensive study investigating the relationship of illicit drug use with musculoskeletal health. Although there was no significant difference in the prevalence of osteoporosis, osteopenia, sarcopenia and fracture among illicit drug users and non-drug users in the male study participants aged ≥60, the null association may be attributed to the small sample size of aged participants in the current study, limiting the statistical power. In this study, we thus focused on investigating the association of illicit drug use with parameters related to bone and muscle health, taking into account the important confounders such as age, sex, physical activity, etc. We showed that illicit drug use was significantly associated with lower BMD and muscle parameters related to sarcopenia. In addition, illicit drug use was significantly associated with reduced PEF, a parameter that reflects both respiratory muscle health and function. These observations suggest that illicit drug users were significantly weaker than the non-drug users in terms of musculoskeletal health.

4.1.1 Illicit drug use and bone health

Most, if not all, published studies evaluated the relationship of individual illicit drug use, instead of any illicit drug use, with BMD. Using the HKOS participants as reference (7), the difference in BMD at the illicit drug users vs non-users was approximately equivalent to -0.41SD (-0.046g/cm^2), -0.37SD (-0.047g/cm^2) and -0.39SD (-0.05g/cm^2) at the lumbar spine, femoral neck, and total hip, respectively. In general, when comparing the estimates observed for all illicit drug users (Table 4) and individual illicit drug groups (Table 5), the magnitude of estimated mean difference observed for all illicit drug users was higher than that for users of narcotics analgesics while lower than that for other non-narcotics analgesic drug groups. This

suggests that narcotics analgesic drugs may have the least impact on BMD among all the illicit drugs examined in the current study.

4.1.1.1 Use of narcotics analgesics and bone health

Narcotics analgesics was the most frequently used illicit drug group in the current study. We could not observe statistically significant association of narcotics analgesics with BMD, which is not consistent with literatures. Previous studies mainly reported poor bone health in men having history of using narcotics analgesics (including opium, heroin, and methadone) (1, 2, 4), while such association in women was inconsistent (4, 12-14). Such discrepancy could be due to difference in the study design and methodology. For example, one previous study used ultrasound in ascertaining the bone health status (12). Yet, ultrasound is known to be inaccurate while the current study used the gold standard DXA in BMD measurement. For men aged under 50 or pre-menopausal women, using BMD T-score for analysis or classification of "osteoporosis" or "osteopenia" were common in literatures (1, 14, 15), but it is not recommended according to the international guidelines (16). Some studies did not include control group for comparison (3, 15) or did not take into account important confounders (1, 3) like physical activity in their analyses. On the other hand, the null association observed in the current study could be because most of the participants with history of using narcotics analgesics were rehabilitees, and the adverse effect of heroin abuse on BMD may be reversed after drug discontinuation (2).

4.1.1.2 Stimulant use and bone health

Stimulants (predominantly methamphetamine, a derivative of amphetamine) were the second most frequently used drug group in the current study. We observed that it was significantly

associated with reduced BMD at all sites measured, which is in line with an earlier study (6) showing that male methamphetamine abusers had a significantly lower BMD at the lumbar spine than non-abusers. We further showed that such decrease in BMD was not only observed at the lumbar spine, but also at the femoral neck and total hip. Indeed, similar reduction in BMD was also observed in amphetamine users (17).

4.1.1.3 Midazolam use and bone health

Although the sample size of midazolam in the current study was small (N=2), a significant association with reduced BMD at the femoral neck and total hip was observed. No prior study has been conducted to investigate the relationship of midazolam with bone health in human, but an *in vitro* study showed that midazolam suppresses osteogenesis in mesenchymal stem cell (18), suggesting midazolam has an adverse effect on BMD. On the other hand, use of benzodiazepine, the drug class that midazolam was classified, was known to be associated with increased risk of hip fracture (19), which could be contributed by its effect on propensity of falls. Together with the current study, benzodiazepine *per se* could have a detrimental effect on bone mass, which may further increase risk of osteoporotic fracture.

4.1.2 Illicit drug use and skeletal muscle health

Musculoskeletal health is not only related to bone health, but also muscle health. Muscle health is known to be a predictor of fracture risk. Similarly, it is also associated with mobility, morbidity, and mortality. The relationship of illicit drug use with muscle health is poorly studied. To the best of our knowledge, only two studies reported that amphetamine (17) and cannabis (20) use reduced muscle strength and slower gait speed among the respective users.

In the current study, we showed that illicit drug use was significantly associated with reduced ALM, gait speed, and handgrip strength, which are the parameters in diagnosing sarcopenia.

ALM, gait speed, and handgrip strength represents muscle mass, function, and strength, respectively. The association of illicit drug use and ALM was mainly driven by the users of hallucinogens, narcotics analgesics, and "others and unknown" drug group (Table 7), since opposite direction of association was observed in the estimated mean difference for the remaining illicit drug groups. For gait speed, users of all illicit drug group, except tranquillizers, had a lower gait speed when compared with non-users, but the only significant association was observed for users of stimulants. A prior study (20) showed that cannabis users had a slower gait speed (0.96m/s) than the non-users (1.26 m/s). In our current study, although a slower gait speed was observed in users of hallucinogens (all cannabis users) (estimated mean: 1.186m/s) than the non-users (estimated mean: 1.236m/s), the difference was not statistically significant. The discrepancy could be explained by the younger age of cannabis users in the current study, while the cannabis users in the previous study were of older age. In addition, we used 6-meter walking test while the previous study used 30-meter walking test. A slower gait speed might be observed in 30-meter test if cannabis affects muscle endurance, while the estimate observed in our 6-meter test is comparatively less affected by muscle endurance. For handgrip strength, users in all illicit drug groups, except those using narcotics analgesics and tranquillizers, had a significantly lower handgrip strength when compared with non-users. The association of stimulant use with reduced handgrip strength is in agreement with a previous study on amphetamine users (17). To our knowledge, no previous studies have examined the association of other illicit drug groups with handgrip strength.

4.2 Illicit drug use and PEF

In addition to skeletal muscle health, we also examined PEF, a parameter reflecting the function and strength of respiratory muscle. This is the first study that investigated the relationship of illicit drug use with PEF. Illicit drug users had a significantly lower PEF. In subgroup analyses for each individual drug groups, except users in depressants and tranquillizers, users in all other illicit drug groups had a significantly lower PEF when compared with non-users. Since muscle health is affected by multiple factors, including comorbidity, inflammation, nervous system, lifestyle, etc, the diminished skeletal and respiratory muscle health observed among illicit drug users could be contributed by the effect of illicit drug on muscle *per se*, or through its effect on other related factors. Notwithstanding the mechanisms, our findings showed that illicit drug users had diminished skeletal and respiratory muscle health when compared to non- users.

4.3 Clinical implications

Our study has important clinical implications. Illicit drug use on musculoskeletal health has been insufficiently investigated, and it remains largely unclear if illicit drug use is associated with impaired musculoskeletal health. In the current study with 108 illicit drug users and 1345 non-users, we clearly showed that illicit drug users had a lower BMD at all sites measured, lower skeletal lean mass, reduced skeletal muscle function and strength. In addition, reduced function and strength were also observed for the respiratory muscle of illicit drug users. Although impaired bone health could be asymptomatic, its clinical outcome, osteoporotic fracture, is known to be associated with increased risk of morbidity, immobility, and mortality. Similarly, impaired muscle health can lead to sarcopenia, which is also known to be associated with poor prognosis and decreased quality of life. Thus, this message should be disseminated widely to the population, which may promote the reduction of illicit drug use and motivate the

intention to quit drug abuse. The finding also implies that musculoskeletal health should be evaluated in drug abusers, and intervention may be warranted to prevent osteoporotic fracture and sarcopenia among illicit drug users and rehabilitees.

4.4 Strengths and limitations

There are several strengths in the current study. We included a large and well-characterised osteoporosis cohort for comparison, providing an ample power for the overall analysis. The illicit drug use history was assessed by an experienced pharmacist in a thorough in-person interview that usually lasted for more than one hour, thus detailed information can be collected. We investigated the important muscle parameters that are never or rarely studied in the literature. Nevertheless, there are limitations. The number of participants in each illicit drug group was small, thus the null association could be due to insufficient power. The small sample size in each illicit drug group also made the analysis of dose and length of drug use on musculoskeletal health infeasible. The number of female drug users included was small, thus sex-specific analysis was not conducted due to limited power. Blood biomarkers of illicit drug use was not evaluated. Future study evaluating the blood-based biomarkers may provide insights to identification of markers that are of diagnostic or therapeutic values.

4.5 Conclusion

Illicit drug users had a significantly lower BMD and diminished muscle health when compared with non-users, implying that they may have elevated risk of morbidity, immobility, and mortality, as well as decreased quality of life. Such findings should be disseminated to the public for motivating the quitting intention of drug abusers and / or reducing illicit drug use. It may also provide the basis for the healthcare professionals to formulate plans to improve the musculoskeletal health of illicit drug users.

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