

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

McGowan, CR; Wright, T; Nitsch, D; Lewer, D; Brathwaite, R; Scott, J; Hope, V; Ciccarone, D; Dunn, J; Gillmore, J; +2 more... Story, A; Harris, M; (2020) High prevalence of albuminuria amongst people who inject drugs: A cross-sectional study. *Scientific Reports*, 10 (1). 7059-. DOI: <https://doi.org/10.1038/s41598-020-63748-4>

Downloaded from: <http://researchonline.lshtm.ac.uk/id/eprint/4656652/>

DOI: <https://doi.org/10.1038/s41598-020-63748-4>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by/2.5/>

<https://researchonline.lshtm.ac.uk>



OPEN

High prevalence of albuminuria amongst people who inject drugs: A cross-sectional study

C. R. McGowan^{1,2}✉, T. Wright¹, D. Nitsch³, D. Lewer⁴, R. Brathwaite⁵, J. Scott⁶, V. Hope⁷, D. Ciccarone⁸, J. Dunn⁹, J. Gillmore¹⁰, A. Story^{4,11} & M. Harris¹

Albuminuria is a key biomarker for cardiovascular disease and chronic kidney disease. Our study aimed to describe the prevalence of albuminuria amongst people who inject drugs in London and to test any potential associations with demographic characteristics, past diagnoses, and drug preparation and administration practices. We carried out a cross-sectional survey amongst people who use drugs in London. The main outcome measure was any albuminuria including both microalbuminuria and macroalbuminuria. Three-hundred and sixteen samples were tested by local laboratory services. Our study initially employed point-of-care testing methods but this resulted in a high number of false positives. Our findings suggest the prevalence of albuminuria amongst PWID is twice that of the general population at 19% (95%CI 15.3–24.0%). Risk factors associated with albuminuria were HIV (aOR 4.11 [95% CI 1.37–12.38]); followed by overuse of acidifier for dissolving brown heroin prior to injection (aOR 2.10 [95% CI 1.04–4.22]). Albuminuria is high amongst people who inject drugs compared to the general population suggesting the presence of increased cardiovascular and renal pathologies. This is the first study to demonstrate an association with acidifier overuse. Dehydration may be common amongst this population and may affect the diagnostic accuracy of point-of-care testing for albuminuria.

People who inject drugs (PWID) may be at risk of serious cardiovascular and kidney diseases, including AA amyloidosis, related to chronic inflammatory conditions and poor overall health. Certain drug injecting practices (e.g. subcutaneous injecting, reuse of injecting equipment) are associated with chronic or recurrent abscesses and other skin and soft tissue infections (SSTIs)¹. Currently, there are few studies looking at early risk markers of cardiovascular disease and chronic kidney disease among PWID, though there is some evidence to suggest that PWID are at increased risk of developing end-stage renal disease^{2–5}. Other injecting practices believed to precipitate inflammation relate to the over-use of acidifiers used to dissolve brown heroin which is the predominant type of heroin available in Europe⁶. It is well established that chronic inflammation is associated with both cardiovascular disease and chronic kidney disease^{7,8}.

Albuminuria is one of the two biochemical markers used to identify the presence of both cardiovascular disease and chronic kidney disease⁹. The presence of albuminuria is a key risk marker for predicting progression to end-stage renal disease, and for identifying other serious sequelae including AA amyloidosis⁹. A person with elevated albuminuria but with normal estimated glomerular filtration rate (eGFR) has the same cardiovascular risk

¹Department of Public Health, Environments & Society, Faculty of Public Health & Policy, London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London, WC1H 9SH, UK. ²Humanitarian Public Health Technical Unit, Save the Children UK, 1 St John's Lane, London, EC1M 4AR, UK. ³Department of Non-communicable Disease Epidemiology, Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. ⁴UCL Collaborative Centre for Inclusion Health, Institute of Epidemiology and Health Care University College London, 1-19 Torrington Place, London, WC1E 7HB, UK. ⁵Department of Social Genetic & Developmental Psychiatry, Institute of Psychiatry, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK. ⁶Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK. ⁷Public Health Institute, Liverpool John Moores University, 79 Tithebarn Street, Liverpool, L2 2ER, UK. ⁸University of California, San Francisco, Department of Family and Community Medicine, 500 Parnassus Avenue, San Francisco, CA, 94143, United States. ⁹Camden & Islington NHS Foundation Trust, 108 Hampstead Road, London, NW1 2LS, UK. ¹⁰National Amyloidosis Centre, Centre for Amyloidosis & Acute Phase Proteins, Division of Medicine, University College London, Rowland Hill Street, London, NW3 2PF, UK. ¹¹University College Hospitals NHS Foundation Trust, 250 Euston Road, London, NW1 2PG, UK. ✉e-mail: Catherine.McGowan@lshtm.ac.uk

as a person with an low eGFR (<60) without albuminuria^{9,10}. Albuminuria has been associated with additional microvascular pathologies (e.g. involving the skin, brain, lungs) which suggests that albuminuria may also be a marker of systemic microvascular disorder¹¹. Albuminuria is associated with cardiovascular risk factors including; overweight/obesity, diabetes, high blood pressure, and tobacco smoking¹⁰.

Population-level estimates reveal a high prevalence of albuminuria in the UK. A 2004 study among those aged 40–79 years in Norfolk, UK estimated the prevalence of microalbuminuria as 11.2% (13.9% in women, 8.1% in men) and macroalbuminuria as 0.7% (0.7% in women, 0.8% in men)¹². The 2009 and 2010 Health Surveys for England estimated that 8% of adults surveyed had abnormal levels of albumin in their urine (7.9% microalbuminuria, 0.5% macroalbuminuria)¹⁰.

This paper aims to describe the prevalence of albuminuria among PWID, and to inform the clinical use and interpretation of albuminuria testing amongst this population.

Methods

We undertook a cross-sectional survey, as part of the UK National Institute for Health Research-funded Care & Prevent study, aimed at assessing the evidence for AA amyloidosis amongst PWID¹³. We developed a computer-assisted questionnaire to identify patterns of drug use and potential risk factors for SSTIs and AA amyloidosis. The questionnaire was conducted with current or past PWID aged 18 years and over who were recruited in London at eight drug treatment services and a mobile health service working with homeless people (UCLH Find & Treat Service). Participants completed the questionnaire followed by a urine screen for albuminuria. Participants were asked questions relating to: demographics, injecting history, injection practices, HIV and hepatitis C virus (HCV) status, SSTI history, and other conditions associated with albuminuria. Potential confounders were age, sex, and tobacco smoking.

Urine was initially tested using laboratory urinalysis and/or point of care (POC) testing using CLINITEK Microalbumin Reagent Strip (Siemens Healthcare GmbH), however, the POC testing yielded a high number of false positives (See **Text Box 1**) and was abandoned in favour of laboratory urinalysis. Albumin levels between 2.8 and 29.9 mg/mmol were considered *abnormal* (i.e. microalbuminuria), and ≥ 30 mg/mmol were deemed *highly abnormal* (i.e. macroalbuminuria). Participants with macroalbuminuria were referred to the University College London (UCL) National Amyloidosis Centre at Royal Free Hospital in North London for diagnostic assessment for AA amyloidosis.

Text Box 1. We initially used CLINITEK Microalbumin 2 Strips in a CLINITEK Status+ Analyser to determine the albumin-to-creatinine ratio (ACR) of urine samples. CLINITEK Microalbumin 2 Strips were selected as they are specified for use with spontaneous urine samples and measure both albumin and creatinine values, enhancing the specificity of results. Despite manufacturer guidelines and reviews assuring adequate specificity and sensitivity for POC testing, we found a discrepancy in 20 of the 45 samples that were also sent for laboratory testing. While POC results indicated albuminuria in 58% of cases (26 micro and 1 macro), laboratory results for the same samples showed 13% with albuminuria (6 micro and 1 macro). (See **Figure 1**) Given this discrepancy we abandoned POC testing. We brought on an additional site with a laboratory pathway, and developed a collaboration with the UCLH Find & Treat Service outreach team, enabling us to recruit through homeless hostels via their outreach team and to use their private laboratory pathway.

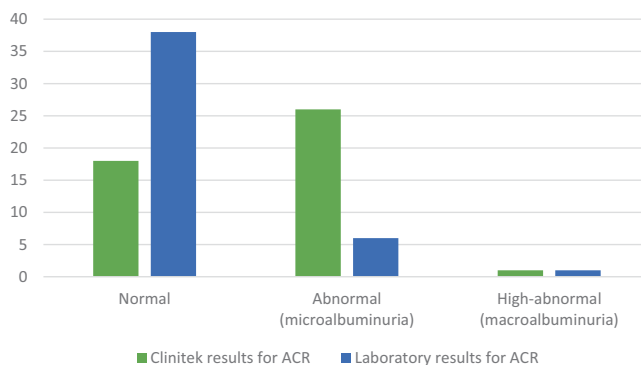


Figure 1. Discrepancy between CLINITEK and laboratory results for ACR.

The discrepancy between POC samples and laboratory samples is likely due to the highly concentrated urines of many participants. Concentrated urine has a very high creatinine level, which would have exceeded the microalbumin strip cut-off point – thus creating a false positive. Highly concentrated urines were also observed on handling, indicating inadequate water consumption and possible dehydration in this population. Aside from the health implications of dehydration, our findings indicate that semi-quantitative POC testing should be avoided or used with extreme caution with this population.

| | N = 316 | % |
|--|---------|------|
| Age | | |
| <35 | 44 | 13.9 |
| 35–44 | 85 | 26.9 |
| 45–54 | 137 | 43.4 |
| >54 | 50 | 15.8 |
| Gender | | |
| Male | 236 | 74.7 |
| Female | 80 | 25.3 |
| Stability of housing in previous 12 months | | |
| Stable (own place, rented) | 136 | 43 |
| Unstable (other people's places, street homeless, hostel dwelling) | 180 | 57 |
| Ever been street homeless | 242 | 76.6 |
| Ethnicity | | |
| White or White British | 230 | 72.8 |
| African, Caribbean or Black British | 39 | 12.3 |
| Asian or Asian British | 7 | 2.2 |
| Mixed ethnicity | 21 | 6.7 |
| Other | 19 | 6 |

Table 1. Participant Characteristics.

Survey data were collected in Open Data Kit (<https://opendatakit.org/>) and transferred into Stata 15 (StataCorp: College Station, TX) for analysis.

All participants were provided with study information sheets and gave written consent prior to answering the questionnaire and providing a sample for urinalysis. Participants were reimbursed for their time with a £10 gift voucher. All methods were carried out in accordance with the relevant guidelines and regulations. This study has been reported against the STROBE reporting checklist for observational studies¹⁴.

Patient and public involvement. The survey was developed in collaboration with the Lambeth and Camden Drug User Forums. Members of the National Amyloidosis Centre Patient Network helped develop the participant information sheets. Groundswell, a local homelessness charity¹⁵, provided input to the study as well as peer support^{16,17} (See GRIPP2 Reporting Checklist **Appendix 1**).

Sample size. We aimed to collect urine samples from 400 participants based on feasibility (rates of service attendance) and an estimated 5% prevalence of proteinuria (95% CI, 3–7%).

Quantitative variables. The main outcomes of interest were any albuminuria; microalbuminuria (a biomarker for other health outcomes, such as cardiovascular disease) and macroalbuminuria (a biomarker for AA-amyloidosis). Exposures were chosen *a priori* as plausible factors in the causal chain and were based on the literature, our clinical experience, and our prior research involving PWID. Exposures include: injecting practices, location of injection sites, number of injection sites used, SSTI history, severity of past or current SSTI, housing status, overuse of acidifier (for dissolving drugs prior to injection), and self-reported lifetime diagnoses of health conditions (e.g. necrotising fasciitis, COPD, sepsis, endocarditis). Smoking status was added to the survey following commencement of data collection owing to the unexpectedly high prevalence of microalbuminuria, and is thus only available for 75% of the total sample, and 95% of the subsample of participants for whom we have laboratory results.

Statistical analysis. Associations between potential risk factors and albuminuria were tested using crude logistic regressions. Bivariate associations found to have a significance of ≤ 0.1 were introduced into the multivariate logistic model to examine independent associations with albuminuria. We used a 95% confidence interval for the calculation of population point estimates of albuminuria. We further estimated a ratio of the prevalence of albuminuria in our PWID sample to the prevalence in the general population using data from the Health Survey for England 2016, which included urinalysis. We fit a poisson regression model on the combined data with albuminuria as the dependent variable and drug injection as the independent variable, adjusting for age group and sex. We then additionally adjusted for smoking status (current, former, or non-smoker).

Ethics Approval. The study was approved by the NHS Health Research Authority (218143), the NHS Research Ethics Committee (17/LO/0872), and the London School of Hygiene & Tropical Medicine Observational Research Ethics Committee (12021–1). Participants gave informed consent to participate in the study.

Results

Of the 455 participants who completed the survey, 442 consented to urinalysis. Three-hundred and sixteen laboratory urinalyses were returned. The 139 samples not included in the analysis were either tested using the POC CLINITEX Microalbumin Reagent Strips only (e.g. for services with no laboratory pathway) or they were rejected

| | N = 316 | % |
|--|---------|------|
| Hepatitis C | 169 | 53.5 |
| Deep Vein Thrombosis (DVT) | 77 | 24.4 |
| Arthritis | 71 | 22.5 |
| Hypertension | 65 | 20.6 |
| Sepsis | 63 | 19.9 |
| Chronic Obstructive Pulmonary Disease (COPD) | 45 | 14.2 |
| Hepatitis B | 40 | 12.7 |
| Liver cirrhosis | 39 | 12.3 |
| Kidney disease | 27 | 8.5 |
| Diabetes | 18 | 5.7 |
| Bone or joint infection | 18 | 5.7 |
| HIV | 17 | 5.4 |
| Endocarditis | 14 | 4.4 |
| Tuberculosis | 13 | 4.1 |
| Necrotising fasciitis | 7 | 2.2 |
| Lymphangitis | 4 | 1.3 |

Table 2. Participant Lifetime Morbidities.

by the laboratory (e.g. the sample container was damaged). We compared the personal characteristics of those from whom we obtained a sample to those from whom we did not using the Mann–Whitney U test (for age) and Pearson χ -squared and found no significant difference between the two groups (See **Appendix 2**).

Descriptive data. The majority of the 316 participants were white (73%) and male (75%), both their mean and median age was 46 years old (IQR 39–52). The average age at first injection drug use was 24 years (See Table 1). Of the 316 participants, 169 (54%) reported a diagnosis of HCV, 77 (24%) deep vein thrombosis (DVT), 45 (14%) chronic obstructive pulmonary disease (COPD), 27 (9%) kidney disease, and seven (2%) necrotising fasciitis. Seventeen (5%) participants reported receiving an HIV diagnosis (See Table 2).

The majority of participants reported having a history of street homelessness ($n = 242$, 77%), with 57% ($n = 180$) currently living in unstable accommodation. The majority reported a typical injecting practice which included injecting one or more times per day ($n = 227$, 72%), and/or injection into the femoral vein (lifetime: $n = 136$, 43%, past 12 months: $n = 62$, 32%) (See Table 3). One-hundred and thirteen (39%) reported over-use of acidifier (defined as more than half a sachet of citric acid or vitamin C⁶) when preparing a £10 bag of heroin. Three hundred participants provided data on smoking status; 272 (91%) reported current or past smoking.

Outcome data. Of the 316 urinalysis results, sixty-one (19.3% [95% CI 15.3–24.0]) were positive for albuminuria with ≥ 2.8 mg/mmol albumin/creatinine ratio. Of these, 52 (16% [95% CI 12.8–21.0]) were classified as having microalbuminuria, and nine (3% [95% CI 1.5–5.4]) had macroalbuminuria. Men and women differed slightly but not significantly: 21.2% (95% CI 16.4–26.9) of men and 15% (95% CI 8.6–24.8) of women were found to have albuminuria. The prevalence of albuminuria generally increased with age: 13.6% (95% CI 6.1–27.7) in participants aged ≤ 35 , and 21.4% (95% CI 16.1–27.9) in those aged ≥ 45 , however this was not significant ($p > 0.05$). The nine participants with macroalbuminuria were referred to the UCL National Amyloidosis Centre and were offered Groundswell peer support (four declined to attend, three attended, and two died before their appointment).

Main results. In a series of crude analyses the following associations were found with albuminuria (See Table 4 for associations): acidifier overuse (OR 1.77, $p = 0.061$), COPD (OR 2.15, $p = 0.033$), HCV (OR 1.86, $p = 0.037$), DVT (OR 1.69, $p = 0.090$), HIV (OR 3.18, $p = 0.025$), and injecting in three body sites (OR 2.49, $p = 0.079$). There was no significant association between SSTIs (OR 0.87, $p = 0.643$) or groin injecting (OR 1.36, $p = 0.282$).

Based on these associations we performed logistic regression using listwise deletion of observations with missing smoking status and adjusted for *a priori* confounders (i.e. age, gender, and current smoking). We found higher odds of having albuminuria amongst those who: reported using more than half a sachet of acidifier per £10 of heroin (aOR 1.71 [95% CI 0.90–3.25]); had been previously diagnosed with COPD (aOR 1.85 [95% CI 0.84–4.06]), HCV (aOR 1.72 [95% CI 0.93–3.20]), HIV (aOR 3.16 [95% CI 1.06–9.41]), and injecting in three body sites (aOR 2.08 [95% CI 0.71–6.06]).

Further adjustment for other covariates suggested that the risk factor with the largest association with albuminuria was HIV (aOR 4.11 [95% CI 1.37–12.38]) followed by over-use of acidifier in injection preparation (aOR 2.10 [95% CI 1.04–4.22]).

In order to determine the age-adjusted prevalence ratio we compared our sample to the Health Survey for England data for 2016. Accounting for smoking status and stratified by age, we excluded the youngest (<25) and oldest (65+) age groups as they included small numbers of observations. The adjusted prevalence ratio suggests that albuminuria is twice as prevalent (1.97 [95% CI 1.49–2.60]) in our population compared to the general population in England.

| | n | % |
|--|-----|------|
| Ever injected psychoactive drugs for non-medical purposes [†] | 316 | 100 |
| Ever injected in arms | 301 | 95.3 |
| Ever injected in hands | 234 | 74.1 |
| Ever injected in legs | 193 | 61.1 |
| Ever injected in feet | 177 | 56 |
| Ever injected in groin | 136 | 43 |
| Ever injected in neck | 119 | 37.7 |
| Ever injected in other | 46 | 14.6 |
| Injected in the last 12 months [‡] | 190 | 60.1 |
| Heroin alone | 136 | 71.6 |
| Heroin and crack | 134 | 70.5 |
| Crack alone | 57 | 30 |
| Powder cocaine | 22 | 11.6 |
| Amphetamine | 16 | 8.4 |
| Ketamine | 10 | 5.3 |
| Other | 6 | 3.2 |
| Prescription diamorphine | 12 | 6.3 |
| Methadone | 6 | 3.2 |
| Mephedrone | 6 | 3.2 |
| Heroin with amphetamines | 9 | 4.7 |
| Steroids or other performance enhancing drugs | 2 | 1.1 |

Table 3. Injection Practices. [†]In order from most commonly identified as ‘main bodysite injected’, to least. [‡]In order from most commonly identified as ‘main drug injected’, to least.

Discussion

Statement of principal findings. This study sought to determine the prevalence of albuminuria amongst PWID in London. Previous studies have estimated that albuminuria in the general adult population in the UK is less than 10%^{12,18,19}. Our findings suggest prevalence amongst PWID is twice that at 19% (15.3–24.0%). However, the age distribution in our sample differs markedly from that of the general adult population¹⁸. Adjusting for current smoking the prevalence ratio decreased to 1.65 (95% CI 1.17–2.31), suggesting that about one-third of the increased prevalence relates to smoking. Within our sample of PWID, overuse of acidifier and HIV were important predictors of albuminuria.

HIV is known to be associated with proteinuric renal lesions²⁰. Additionally, we hypothesise that persistent overuse of acidifier in injection solution is precipitating venous sclerosis (owing to endothelial stress), thus complicating venous access and resulting in multiple venous injection attempts (and possible *accidental* subcutaneous injecting) and/or transition to *intentional* subcutaneous injecting²¹. Subcutaneous injecting introduces substances and/or bacteria directly into tissues which, in turn, causes persistent localised inflammation¹. Alternatively, we cannot rule out the possibility that over-use of acidifier is directly causing local or systemic inflammation⁶. Chronic inflammation is strongly associated with cardiovascular and renal disease of which albuminuria is a biomarker⁹.

These data suggest that PWID are a high-risk group to develop cardiovascular and renal complications. A recent study of mortality among people who use heroin in South London found 2.8 times the risk of cardiovascular mortality compared to the general population²². If the associations (as observed in the general UK population) between albuminuria and future risk of cardiovascular disease are also true for PWID, one would expect the stroke risk in this population to be increased by 90% relative to a person with no albuminuria²³, whilst the absolute risk of cardiovascular mortality increases by about 30% for a doubling of albuminuria²⁴.

Strengths and weaknesses of the study. Initially, urine sample testing was carried out using a POC testing machine; however, false positives were identified following confirmatory laboratory testing. We believe this to be a result of high levels of dehydration amongst PWID. Our prevalence estimate may have been improved by testing twice (as per NICE guidelines); however, this would have been difficult given our study population⁹. The Health Survey for England albuminuria data were collected based on the same protocol used for the present study (i.e. a single sample) therefore increasing its comparability with our study population¹⁸.

The absence of a significant association between SSTIs and albuminuria was surprising as we anticipated SSTIs would be a key factor in activating the inflammatory cascade. It is possible that our participants underreported past SSTIs or that our sample was underpowered to draw out this association. Our study may also have been underpowered to detect other meaningful predictor variables. Finally, we cannot rule out the possibility that HIV and excessive use of acidifier may be contributing to a systemic microvascular disorder.

Unanswered questions and future research. Future studies should investigate long-term outcomes of PWID related to cardiovascular and renal risk, though we appreciate the challenges of following up a difficult to capture population. Future trials should investigate whether cardiovascular and renal disease may be delayed by blood pressure lowering therapy or a poly-pill (i.e. a pill containing a combination of several medications) in

| Variable | Albuminuria (micro/macro) | | Crude OR (95% CI) | Adjusted* AOR (95% CI) | Multiple adjusted** AOR (95% CI) |
|--------------------------------------|---------------------------|----------|----------------------|---------------------------|--|
| | NO (%) | YES (%) | | | |
| Reuse needles and syringes | | | | | |
| No | 79 (81%) | 18 (19%) | 1 | — | — |
| Yes | 176 (80%) | 43 (20%) | 1.07 (0.58–1.98) | — | — |
| Reuse filters | | | | | |
| No | 109 (80%) | 28 (20%) | 1 | — | — |
| Yes | 140 (82%) | 30 (18%) | 0.83 (0.47–1.48) | — | — |
| Injecting frequency per week | | | | | |
| Once | 30 (77%) | 9 (23%) | 1 | — | — |
| 2–3 times a week | 28 (85%) | 5 (15%) | 0.60 (0.18–2.00) | — | — |
| 4–6 times a week | 13 (76%) | 4 (24%) | 1.03 (0.27–3.95) | — | — |
| Once a day | 28 (80%) | 7 (20%) | 0.83 (0.27–2.54) | — | — |
| 2–3 times a day | 99 (84%) | 19 (16%) | 0.64 (0.26–1.56) | — | — |
| ≥ Four times a day | 57 (77%) | 17 (23%) | 0.99 (0.40–2.50) | — | — |
| Current smoker | | | | | |
| No | 25 (89%) | 3 (11%) | 1 | — | — |
| Yes | 221 (81%) | 51 (19%) | 1.92 (0.56–6.63) | — | — |
| Ever inject in hands | | | | | |
| No | 69 (84%) | 13 (16%) | 1 | — | — |
| Yes | 186 (79%) | 48 (21%) | 1.37 (0.70–2.69) | — | — |
| Ever inject in arms | | | | | |
| No | 13 (87%) | 2 (13%) | 1 | — | — |
| Yes | 242 (80%) | 59 (20%) | 1.58 (0.35–7.23) | — | — |
| Ever inject in feet | | | | | |
| No | 115 (83%) | 24 (17%) | 1 | — | — |
| Yes | 140 (79%) | 37 (21%) | 1.27 (0.72–2.24) | — | — |
| Ever inject in legs | | | | | |
| No | 102 (83%) | 21 (17%) | 1 | — | — |
| Yes | 153 (79%) | 40 (21%) | 1.27 (0.71–2.28) | — | — |
| Ever inject in groin | | | | | |
| No | 149 (83%) | 31 (17%) | 1 | — | — |
| Yes | 106 (78%) | 30 (22%) | 1.36 (0.78–2.38) | — | — |
| Number of sites ever injected | | | | | |
| One | 56 (86%) | 9 (14%) | 1 | 1 | 1 |
| Two | 35 (83%) | 7 (17%) | 1.24 (0.42–3.65) | 1.16 (0.40–3.35) | 0.73 (0.18–2.91) |
| Three | 25 (71%) | 10 (29%) | 2.49 (0.90–6.89) | 2.08 (0.71–6.06) | 3.01 (0.98–9.22) |
| Four or more | 139 (80%) | 35 (20%) | 1.57 (0.71–3.48) | 1.36 (0.61–3.00) | 1.53 (0.64–3.64) |
| Ever had SSTI | | | | | |
| No | 82 (80%) | 20 (20%) | 1 | — | — |
| Yes | 173 (81%) | 41 (19%) | 0.97 (0.54–1.76) | — | — |
| Severity of infection | | | | | |
| Mild/moderate | 85 (80%) | 21 (20%) | 1 | — | — |
| Severe | 65 (80%) | 16 (20%) | 1.00 (0.48–2.06) | — | — |
| Unstable housing | | | | | |
| No | 113 (83%) | 23 (17%) | 1 | — | — |
| Yes | 142 (79%) | 38 (21%) | 1.31 (0.74–2.33) | — | — |
| Acidifier overuse | | | | | |
| No | 152 (85%) | 27 (15%) | 1 | 1 | 1 |
| Yes | 86 (76%) | 27 (24%) | 1.77 (0.97–3.21) | 1.71 (0.90–3.25) | 2.10 (1.04–4.22) |
| Diagnoses of health condition | | | | | |
| HIV | | | | | |
| No | 245 (82%) | 54 (18%) | 1 | 1 | 1 |
| Yes | 10 (59%) | 7 (41%) | 3.18 (1.16–8.73) | 3.16 (1.06–9.41) | 4.11 (1.37–12.38) |
| HCV | | | | | |
| No | 126 (86%) | 21 (14%) | 1 | 1 | 1 |
| Yes | 129 (76%) | 40 (24%) | 1.86 (1.04, 3.33) | 1.72 (0.93–3.20) | 2.07 (0.99–4.31) |
| Continued | | | | | |

| Variable | Albuminuria (micro/macro) | | Crude | Adjusted* | Multiple adjusted** |
|----------|---------------------------|----------|------------------|-------------------|---------------------|
| | NO (%) | YES (%) | OR (95% CI) | AOR (95% CI) | AOR (95% CI) |
| DVT | | | | | |
| No | 198 (83%) | 41 (17%) | 1 | 1 | — |
| Yes | 57 (74%) | 20 (26%) | 1.69 (0.92–3.12) | 1.37 (0.70, 2.67) | — |
| COPD | | | | | |
| No | 224 (83%) | 47 (17%) | 1 | 1 | 1 |
| Yes | 31 (69%) | 14 (31%) | 2.15 (1.06–4.36) | 1.85 (0.84–4.06) | 1.97 (0.86–4.50) |

Table 4. Associations Between Albuminuria and Risk Factors. *Adjusted for age, gender, and smoking. **Stepwise model adjusted for: age, gender, smoking, number of injection sites, over-use of acidifier, HIV, HCV, COPD.

those with albuminuria. In addition, studies could explore the reversibility of albuminuria through risk reduction and/or entry into substance use treatment (e.g. opioid agonist therapy). We encourage evaluations of the efficacy and cost-effectiveness of albuminuria screening amongst PWID.

Conclusion

Albuminuria is twice as prevalent among PWID compared to the general population and may identify those with high cardiovascular and renal risk. Clinicians, such as general practitioners, should be aware of the risk and consider albuminuria testing of PWID. Finally, dehydration may be common amongst PWID and may affect the diagnostic accuracy of POC testing for albuminuria. We encourage careful interpretation of albuminuria tests among this population.

APPENDIX 1: GRIPP2 Short Form

| Section and topic | Item | Reported on page No |
|-------------------------------------|---|---------------------|
| 1: Aim | Report the aim of PPI in the study | 3 |
| 2: Methods | Provide a clear description of the methods used for PPI in the study | 3 |
| 3: Study results | Outcomes—Report the results of PPI in the study, including both positive and negative outcomes | 5 |
| 4: Discussion and conclusions | Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects. | n/a |
| 5: Reflections/critical perspective | Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience | n/a |

APPENDIX 2: Table comparing demographics for those with and without an ACR result

| | ACR result | | No ACR result | | Pearson's chi squared | | Mann Whitney U | |
|--|------------|------|---------------|------|-----------------------|---------|----------------|---------|
| | N = 316 | % | N = 139 | % | χ^2 (df) | P value | z | P value |
| Age | | | | | | | 1.3 | 0.194 |
| <35 | 44 | 13.9 | 21 | 15.1 | | | | |
| 35–44 | 85 | 26.9 | 45 | 32.4 | | | | |
| 45–54 | 137 | 43.4 | 57 | 41 | | | | |
| >55 | 50 | 15.8 | 16 | 11.5 | | | | |
| Gender | | | | | 0.04 (1) | 0.846 | | |
| Male | 236 | 74.7 | 105 | 75.5 | | | | |
| Female | 80 | 25.3 | 34 | 24.5 | | | | |
| Stability of housing in previous 12 months | | | | | 0.07 (1) | 0.794 | | |
| Stable (own place, rented) | 136 | 43 | 58 | 41.7 | | | | |
| Unstable (other people's places, street homeless, hostel dwelling) | 180 | 57 | 81 | 58.3 | | | | |
| Ever been street homeless | 242 | 76.6 | 113 | 81.3 | 1.25 (1) | 0.263 | | |
| Ethnicity | | | | | 4.00 (4) | 0.407 | | |
| White or White British | 230 | 72.8 | 106 | 76.3 | | | | |
| African, Caribbean or Black British | 39 | 12.3 | 11 | 7.9 | | | | |
| Asian or Asian British | 7 | 2.2 | 5 | 3.6 | | | | |
| Mixed ethnicity | 21 | 6.7 | 6 | 4.3 | | | | |
| Other | 19 | 6 | 11 | 7.9 | | | | |

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Received: 18 December 2019; Accepted: 30 March 2020;

Published online: 27 April 2020

References

- Murphy, E. L. *et al.* Risk Factors for Skin and Soft-Tissue Abscesses among Injection Drug Users: A Case-Control Study. *Clin. Infect. Dis.* **33**, 35–40, <https://doi.org/10.1086/320879> (2001).
- Scott, J. K., Taylor, D. M. & Dudley, C. R. K. Intravenous drug users who require dialysis: causes of renal failure and outcomes. *Clin. Kidney J.* **11**, 270–274, <https://doi.org/10.1093/ckj/sfx090> (2018).
- Perneger, T. V., Klag, M. J. & Whelton, P. K. Recreational drug use: a neglected risk factor for end-stage renal disease. *Am. J. Kidney Dis.* **38**, 49–56, <https://doi.org/10.1053/ajkd.2001.25181> (2001).
- Hileman, C. O. & McComsey, G. A. The Opioid Epidemic: Impact on Inflammation and Cardiovascular Disease Risk in HIV. *Curr. HIV/AIDS Rep.* **16**, 381–388, <https://doi.org/10.1007/s11904-019-00463-4> (2019).
- Harris, M. *et al.* Drawing attention to a neglected injecting-related harm: a systematic review of AA amyloidosis among people who inject drugs. *Addiction* **113**, 1790–1801, <https://doi.org/10.1111/add.14257> (2018).
- Harris, M. *et al.* Injecting-related health harms and overuse of acidifiers among people who inject heroin and crack cocaine in London: a mixed-methods study. *Harm Reduct. J.* **16**, 60, <https://doi.org/10.1186/s12954-019-0330-6> (2019).
- Mihai, S. *et al.* Inflammation-Related Mechanisms in Chronic Kidney Disease Prediction, Progression, and Outcome. *J. Immunol. Res.* **2018**, 2180373–2180373, <https://doi.org/10.1155/2018/2180373> (2018).
- Golia, E. *et al.* Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. *Curr. atherosclerosis Rep.* **16**, 435, <https://doi.org/10.1007/s11883-014-0435-z> (2014).
- National Institute for Health and Care Excellence (NICE). *Chronic kidney disease in adults: assessment and management*, <https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations> (2015).
- Fraser, S. D. S. *et al.* Chronic kidney disease, albuminuria and socioeconomic status in the Health Surveys for England 2009 and 2010. *J. Public Health* **36**, 577–586, <https://doi.org/10.1093/pubmed/fdt117> (2013).
- Barzilay, J. I. *et al.* Hospitalization Rates in Older Adults With Albuminuria: The Cardiovascular Health Study. *The Journals of Gerontology: Series A*, <https://doi.org/10.1093/geron/glaa020> (2020).
- Yuyun, M. F. *et al.* Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int. J. Epidemiol.* **33**, 189–198, <https://doi.org/10.1093/ije/dyh008> (2004).
- Harris, M. *et al.* ‘Care and Prevent’: rationale for investigating skin and soft tissue infections and AA amyloidosis among people who inject drugs in London. *Harm Reduction Journal* **15**, 23, <https://doi.org/10.1186/s12954-018-0233-y> (2018).
- Equator Network. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. (University of Oxford, Oxford, 2019).
- Groundswell. *Groundswell: Out of homelessness*, <http://groundswell.org.uk> (2019).
- Hepatitis C Trust. *The Hepatitis C Trust*, <http://www.hepctrust.org.uk> (2019).
- University College London Hospitals. *Find & Treat service*, <https://www.uclh.nhs.uk/OurServices/ServiceA-Z/HTD/Pages/MXU.aspx> (2019).
- Fat, L., Mindell, J. & Roderick, P. Health Survey for England 2016 Kidney and liver disease. (Health and Social Care Information Centre, London, 2017).
- Tillin, T., Forouhi, N., McKeigue, P. & Chaturvedi, N. Microalbuminuria and coronary heart disease risk in an ethnically diverse UK population: a prospective cohort study. *J. Am. Soc. Nephrol.* **16**, 3702–3710, <https://doi.org/10.1681/asn.2005060584> (2005).
- Fine, D. M., Perazella, M. A., Lucas, G. M. & Atta, M. G. Renal disease in patients with HIV infection: epidemiology, pathogenesis and management. *Drugs* **68**, 963–980, <https://doi.org/10.2165/00003495-200868070-00006> (2008).
- Ciccarone, D. & Harris, M. Fire in the vein: Heroin acidity and its proximal effect on users’ health. *Int. J. Drug Policy* **26**, 1103–1110, <https://doi.org/10.1016/j.drugpo.2015.04.009> (2015).
- Lewer, D., Tweed, E. J., Aldridge, R. W. & Morley, K. I. Causes of hospital admission and mortality among 6683 people who use heroin: A cohort study comparing relative and absolute risks. *Drug Alcohol Dependence* **204**, 107525, <https://doi.org/10.1016/j.drugalcdep.2019.06.027> (2019).
- Lee, M. *et al.* Impact of microalbuminuria on incident stroke: a meta-analysis. *Stroke* **41**, 2625–2631, <https://doi.org/10.1161/STROKEAHA.110.581215> (2010).
- Hillege, H. L. *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* **106**, 1777–1782, <https://doi.org/10.1161/01.cir.0000031732.78052.81> (2002).

Acknowledgements

We would like to thank all service users and staff at the following services: Margarete Centre, Lorraine Hewitt House, Better Lives, Response, Find & Treat, Turning Point (Hammersmith, Chelsea & Kensington, and Westminster). Thank you also to Kate Johnstone and Harry Clark from the Camden and Islington research team for their help with recruitment. Additional thanks to Jim Conneely for his ongoing support for the study. Thank you also to Drs Shirley Huchcroft and Louisa Baxter for their advice on the analysis. Finally, we would like to reiterate our gratitude to our research participants who have been exceptionally generous with their time. The study was funded by the UK National Institute for Health Research (CDF-2016–09–014). The funder did not play a role in: the development of the study design; the collection, analysis, and interpretation of data; or the writing of the manuscript and the decision to submit the manuscript for publication. All authors, both internal and external, had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Magdalena Harris is funded by a National Institute for Health Research (NIHR), Career Development Fellowship for this research project. This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Dr Ciccarone acknowledges research funding support from the US National Institutes of Health, National Institute on Drug Abuse (R01DA037820).

Author contributions

Conceptualisation: CM/TW/VH/DC/JD/JG/AS/MH Data curation: TW/RB Formal analysis: CM/TW/DN/DL/DC Funding acquisition: MH Investigation: CM/TW/RB/JD/AS/MH Methodology: CM/DN/DL/JS/VH/DC/MH Project administration: CM/RB/MH Resources: JD/JG/MH Software: TW/DL Supervision: DN/RB/MH Writing-original draft: CM/TW/DN/DL/JS/VH/DC/JD/JG/AS/MH Writing-review & editing: CM/TW/DN/DL/MH.

Competing interests

Dr. McGowan reports personal fees from European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) outside the submitted work. Dr. Nitsch reports other grants from Glaxo Smith Kline, outside the submitted work. Dr. Scott reports other from Turning Point, other from Cognisant Research, non-financial support from Academy of Medical Sciences, grants from Medical Research Council, grants from Pharmacy Research UK, outside the submitted work. Dr. Ciccarone reports grants from the US National Institutes of Health, National Institute on Drug Abuse, during the conduct of the study; personal fees from Malinckrodt, personal fees from Nektar Therapeutics, personal fees from Celero Systems, personal fees from American Association for the Advancement of Science, outside the submitted work. The remaining authors declare no competing interests.

Additional information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41598-020-63748-4>.

Correspondence and requests for materials should be addressed to C.R.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2020