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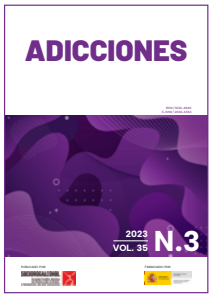

ORIGINAL

A 35-year follow-up study of patients admitted to methadone treatment between 1982-1984 in Asturias, Spain

Estudio de seguimiento de 35 años de pacientes admitidos a tratamiento con metadona entre 1982-1984 en Asturias, España

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Abstract

The objective was to evaluate outcomes in a heroin-dependent population 35 years after first enrolment in methadone maintenance treatment (MMT). An ad hoc protocol was used to assess drug misuse, treatment, and drug-related morbidity in the survivor sample. The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated. A total of 214 heroin-dependent patients entered MMT between 1982 and 1984 in the Asturias Public Health Service. Information was received on 195 subjects, of whom 146 were deceased. Men accounted for 77.5% of the study cohort. Over the 35-year follow-up period, the SMR was 11.75 (95% CI = 9.95 - 13.77). In the survivor sample, 5.7% were still enrolled in MMT; human immunodeficiency virus (HIV) was diagnosed in 38.77% and hepatitis B/C in 73.46%. No sex differences were found for mortality or HIV and hepatitis B/C status. None of the female survivors were using heroin at the 35-year follow-up, compared with 5.26% of males. In conclusion, our study confirms the high long-term mortality rate of heroin addicts, even after enrollment in MMT.

Keywords: mortality, heroin addiction, methadone maintenance therapy, follow-up

Resumen

El objetivo fue evaluar el estado de una población dependiente a la heroína 35 años después de su primera inscripción en un tratamiento de mantenimiento con metadona (TMM). Se utilizó un protocolo ad hoc para evaluar morbilidad, consumo y tratamiento de la adicción en la muestra de supervivientes. Se calculó la razón de mortalidad estandarizada (RME) con un intervalo de confianza (IC) del 95%. Un total de 214 pacientes ingresaron en TMM entre 1982 y 1984 en el Servicio de Salud Pública de Asturias. Se recibió información sobre 195 sujetos, de los cuales 146 habían fallecido. Los hombres representaron el 77,5% de la cohorte del estudio. Durante el período de seguimiento de 35 años, la RME fue de 11,75 (IC 95% = 9,95 – 13,77). En la muestra de supervivientes, el 5,7% todavía estaba inscrito en TMM; el virus de inmunodeficiencia humana (VIH) se diagnosticó en un 38,77% y la hepatitis B/C en un 73,46%; el consumo actual de heroína se informó en un 4,1%. No hubo diferencias de género en la mortalidad o la condición de VIH y hepatitis B/C. Ninguna de las mujeres consumía heroína en el seguimiento de 35 años en comparación con el 5,26% de los hombres. En conclusión, nuestro estudio confirma la alta tasa de mortalidad a largo plazo, incluso después de la inscripción en TMM.

Palabras clave: mortalidad, adicción a la heroína, tratamiento de mantenimiento con metadona, seguimiento

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Heroin addiction is a chronic, relapsing disease that causes medical, social, and economic problems. There are three types of factors that contribute to the development of heroin dependence: environmental, drug-induced, and genetic (Hser, Hoffman, Grella & Anglin, 2001; Randesi et al., 2016). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimates the prevalence of opiate use in Europe at 0.4%, the equivalent of 1.3 million adults. However, these data suggest that in the European Union, prevalence rates of use have decreased in recent years (EMCDDA, 2019).

One of the main treatments for heroin dependence in many countries is methadone maintenance treatment (MMT) (Hall, Lynskey & Degenhardt, 2002). This treatment was started as a research project in 1964 (Dole, Nyswander & Kreek, 1966; Dole, 2008) and has subsequently been replicated in programs throughout the world (Novick et al., 1993).

The greater retention of patients in MMT, compared with other treatments, indicates the effectiveness of this intervention in different population (Mattick, Breen, Kimber & Davoli, 2009; Maremmani et al., 2018; Sutlovic et al., 2018). There are diverse factors associated with this retention, including the prescribed dose and presence of infectious diseases (Adelson et al., 2013). Studies have also shown the positive effects of MMT, including reduced illicit opioid use, risk of human immunodeficiency virus (HIV) infection, and illegal activities, and improved overall functioning and mental and physical health (Holland et al., 2013; Kleber, 2008; Mattick et al., 2009; Soyka, Strehle, Rehm, Bühringer & Wittchen, 2017; Ward, Hall & Mattick, 1999; Wang et al., 2014). In addition, stabilizing patients in MMT programs gives them a better chance of finding and holding a suitable job and improves their family and social relationships, as well as their quality of life (Lin, Wu & Detels, 2011).

Mortality among opioid-dependent users varies across countries and populations, but drug overdose is the leading cause of death (Degenhardt et al., 2011; Evans et al., 2015; Russolillo, Moniruzzaman & Somers, 2018; Sutlovic et al., 2018), while medical comorbidities, such as HIV infection, were also associated with an increased mortality rate (Nosyk et al., 2015). MMT is clearly protective against mortality, even in non-randomized observational studies (Clausen, Anchersen & Waal, 2008; Degenhardt et al., 2011; Esteban et al., 2003; Marotta & McCullagh, 2017; Nosyk et al., 2015; Sordo et al., 2017). In the last decade, follow-up studies show that patients in MMT have a 1-year mortality rate between 1% and 1.63% (Cousins et al., 2016; Russolillo et al., 2018; Soyka et al., 2017), while the annual death rate in young adult opiate abusers is around 2% to 6% per year (Darke, Mills, Ross & Teesson, 2011; Degenhardt et al., 2011).

Despite this, the induction phase of methadone treatment and the time immediately after leaving treatment are periods of particularly high mortality risk (Cousins et al., 2016; Evans et al., 2015; Sordo et al., 2017). Furthermore, high rates of mental illness, cocaine and benzodiazepine abuse, sleep disorders, and disruptive behavior are problems that persist in many MMT programs (Dunn, Finan, Tompkins & Strain, 2018; Maremmani et al., 2018; Nordmann et al., 2016; Motta-Ochoa, Bertrand, Arruda, Jutras-Aswad & Roy, 2017; Potik, Abramsohn, Schreiber, Adelson & Peles, 2020).

Relatively little is currently known about long-term recovery processes among addicts who do achieve and maintain abstinence, their needs, and the impact and suitability of MMT, as there are few long-term follow-up studies on this type of patient (Evans et al., 2015; Hser, Evans, Grella, Ling & Anglin, 2015; Jimenez et al., 2000; Jimenez et al., 2011). This may be related to low patient retention in treatment, making longitudinal research very difficult (Hser et al., 2015; Zhou & Zhuang, 2014). Therefore, the aim of our work was to evaluate outcome in a heroin-dependent population 35 years after their first enrollment in MMT. More specifically, we assessed mortality, current drug use, treatment, drug-related morbidity, socioeconomic level, and legal disability in survivors.

Method

Design and sample

This was an observational 35-year follow-up study in a sample of 214 heroin-dependent patients who entered MMT in the Asturias Public Health Service between 1982 and 1984. They were the first patients to be enrolled in MMT in Asturias. Inclusion criteria for enrollment in MMT were (1) severely ill patients with a poor prognosis; (2) patients older than 18 years of age; and (3) patients with two therapeutic failures.

The MMT program in Asturias is a universal program, integrated into the public assistance network, which is easily accessed through Primary Care and Mental Health Services. It is a medium-demand program, as there is no waiting list, time limitation of treatment, or methadone dosage limit. The reasons for expulsion are verbal or physical violence, and drug trafficking or consumption within the center.

The first interview took place at the time of enrollment in MMT. The data were collected by means of an ad hoc protocol on drug dependence, including sociodemographic, clinical, family, job, and legal data. All subjects who presented for treatment were included in the sample, even if they left treatment prematurely.

Follow-up procedure

At the 15- and 25-year follow-up, patients were contacted by telephone. Data were collected via telephone interviews

and/or review of medical records. The main findings from the 15- and 25-year follow-up are reported elsewhere (Jimenez et al., 2000; Jimenez et al., 2011).

The 35-year follow-up is the main subject of the present work. Before the assessment, we made an extensive effort to find the patients. Patients were invited to participate in the study via telephone interview conducted by members of the research team.

A trained research psychologist assessed the interviews. Additional data was obtained from medical records and from the Spanish Population and Health Resources Information System (SIPRES) that collects sociodemographic information (date of birth, personal address, employment status and living situation). A total of 19 subjects (8.8%) could not be located. Information was therefore obtained on 195 subjects (91.1%), of whom 3 (1.5%) refused an interview and 146 (74.8%) had died. In all, 46 (23.5%) subjects were interviewed.

Number of deaths

We received information about the number of deaths from the Spanish Ministry of Health death register and from the SIPRES. Information on cause of death was collected via direct personal interviews of relatives or by a review of medical records, resulting in incomplete data.

Measures

An ad hoc protocol was used to collect data on the use of addiction treatment resources. Actual drug misuse was assessed via personal interview. Information concerning patient HIV and HBV/HCV status was obtained via personal interview and from medical records.

Statistical Analyses

Our aim was to determine whether the study sample of heroin-dependent patients had a survival rate comparable to the demographically matched general population, according to the 2018 results provided by Spain's National Statistics Institute (Instituto Nacional de Estadística, 2018). The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated using the expected number of deaths in the sample, according to demographic statistics for the overall population. The null hypothesis was tested using a one-sample log-rank test. Additionally, Kaplan-Meier curves were constructed, which showed the expected and observed results. In order to assess the annual death rate for each year of age during follow-up, we used the convention proposed by Finkelstein, Muzikansky & Schoenfeld (2003) that both diagnosis and end of follow-up occurred on a patient's birthday. All calculations were performed using R statistical software, version 3.6.1 (R Core Team, 2019). Mean comparisons between two groups were performed using the t-test for normally distributed independent samples. Nonparametric tests were used as necessary. When comparing categorical data, chi-square (χ^2) tests were used. Finally, a logistic regression model (forward stepwise selection) was estimated to determine the independent factors associated with dying in the last 20 years. The level of statistical significance was set at $\alpha = 0.05$ (two-tailed).

Ethics

The study was conducted in compliance with Spanish national legislation. It was approved by the Clinical Research Ethics Committee of Hospital Universitario Central de Asturias, Oviedo, Spain (ref. no. 52/19) and was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (World Medical Association, 1989).

Results

Baseline versus follow-up samples

Demographic and clinical characteristics of survivors (n=49) compared with previous data are shown in Table 1, Table 2, and Fig. 1. Men accounted for 76.2% (n=163)

Table 1
Clinical characteristics of survivors at follow-up

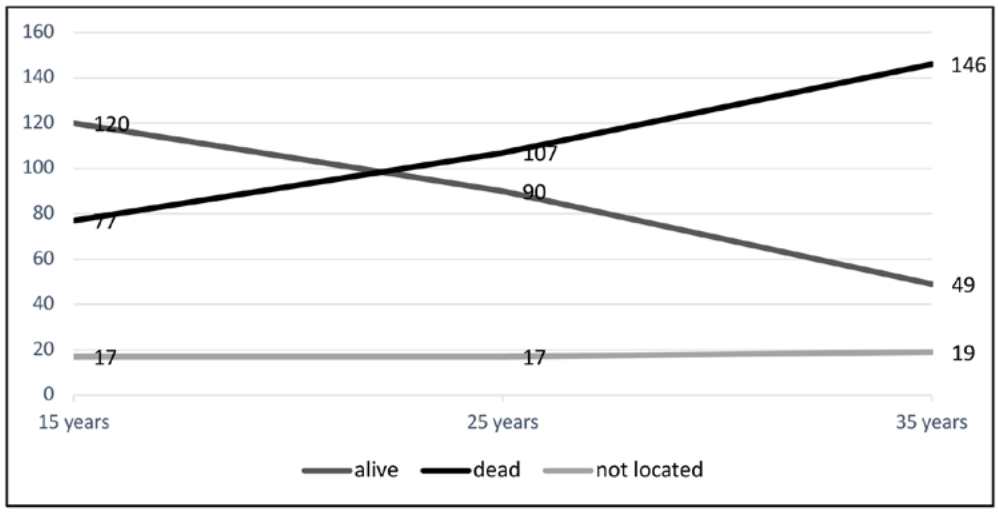
	Baseline (N=214)		15 years (N=120)		25 years (N=90)		35 years (N=49)	
Sex	Men 78.1%	Women 21.9%	Men 77.5%	Women 22.5%	Men 77.8%	Women 22.2%	Men 77.60%	Women 22.40%
Age (SD)	26.05 (8.57)	25.29 (4.30)	40.16 (7.58)	38.81 (3.27)	50.13 (7.19)	49.05 (3.67)	61.61 (9.22)	59.27 (3.85)
HIV+	No data	No data	45.6%	47.1%	37.1%	35.0%	42.1%	27.3%
HBV/HCV	No data	No data	68.2%	70.0%	65.7%	60.0%	76.3%	63.6%
Current heroin	100%	100%	51.1%*	20.0%*	32.5%*	0%*	5.26%	0%
Current MMT	100%	100%	72.5%	84.6%	50.0%	37.5%	5.7%	0%

Note. *Men vs. women difference $p<0.05$. MMT=methadone maintenance treatment; Fisher's exact test: Heroin: $p = 1$, MMT: $p = 1$; Chi-square: HBV/HCV: $\chi^2 = 1.977$, $p = 0.372$; HIV: $\chi^2 = 0.808$, $p = 0.668$.

Table 2
Sociodemographic characteristics of survivors at follow-up

	15 years (N = 120)			35 years (N = 49)		
Sex	Men (n = 93)	Women (n = 27)	Total (N = 120)	Men (n = 38)	Women (n = 11)	Total (N = 49)
Education level [n (%)]						
Primary	17 (56.7)	3 (30.0)	20 (50.0)	9 (52.9)	1 (25.0)	10 (47.6)
Secondary	11 (36.7)	6 (60.0)	17 (47.2)	6 (35.3)	3 (75.0)	9 (42.9)
University	2 (6.7)	1 (10.0)	3 (7.5)	2 (11.8)	--	2 (9.5)
Work status [n (%)]						
Working	17 (50.0)	4 (40.0)	21 (47.7)	11 (34.4)	3 (30.0)	14 (33.3)
Unemployed	7 (20.6)	3 (11.1)	10 (22.7)	3 (9.4)	1 (10.0)	4 (9.5)
Retired	10 (29.4)	2 (7.4)	12 (27.3)	18 (56.2)	6 (10.0)	24 (57.1)
Student	--	1 (3.7)	1 (2.3)	--	--	--
Legal disability [n (%)]						
Yes	14 (16.1)	3 (11.1)	17 (14.9)	12 (33.3)	2 (18.2)	24 (29.8)
No	12 (13.8)	5 (18.5)	17 (14.9)	5 (13.9)	2 (18.2)	7 (14.9)
Unknown	61 (70.1)	19 (70.4)	80 (70.2)	19 (52.8)	7 (63.6)	26 (55.3)
Marital status [n (%)]						
Married	22 (61.1)	7 (58.3)	29 (61.7)	4 (36.4)	1 (33.3)	5 (35.7)
Never married	9 (25.0)	–	9 (19.1)	3 (27.3)	--	3 (21.4)
Separated/Divorced	3 (8.4)	3 (27.3)	6 (12.8)	3 (27.3)	1 (33.3)	4 (28.6)
Widowed	2 (5.6)	1 (9.1)	3 (6.4)	1 (9.1)	1 (33.3)	2 (14.3)

Figure 1
35-year follow-up



of the study cohort and had a mean age of 26.05 years (SD=8.57) at their first interview. Women accounted for 23.8% (n=38) of the study cohort and had a mean age of 25.29 years (SD=4.31). There was no difference in mean age between men and women (Kruskal-Wallis test, p=0.594).

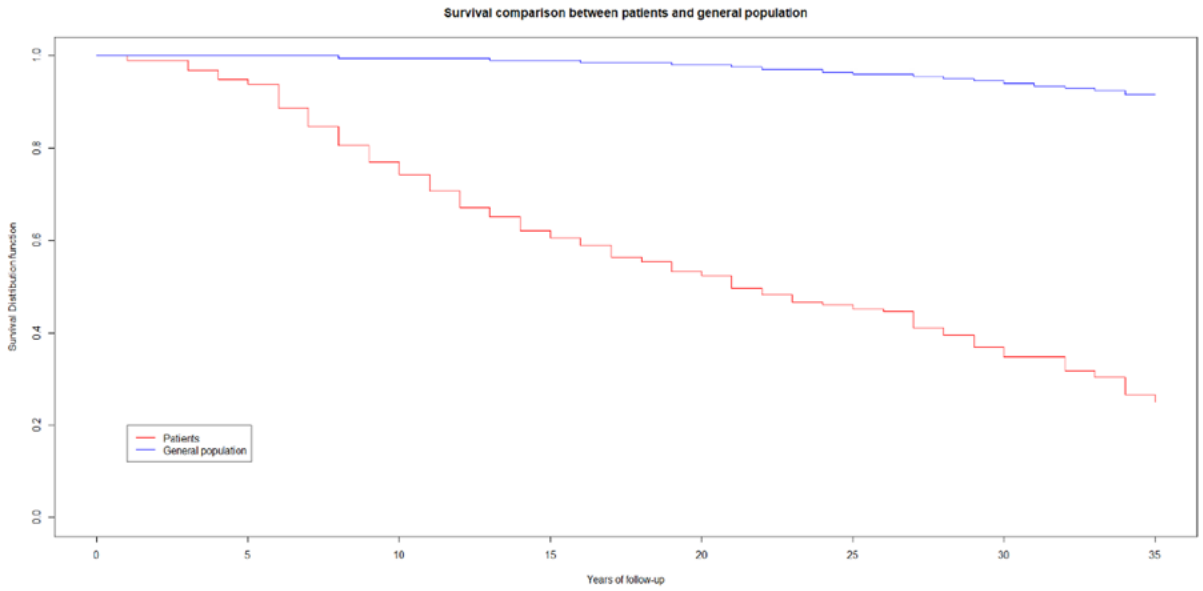
Men accounted for 77.6% (n=38) of the survivor cohort and 88.4% (n=129) of the deceased cohort. Women accounted for 22.4% (n=11) of the survivor cohort and 24.7% (n=36) of the deceased cohort. There was no difference in sex distribution of the survivors and deceased cohorts (χ^2=0.0321, p=0.8578).

HIV/Hepatitis B status

Overall, 38.77% (n=19) of the survivors had an HIV diagnosis at the 35-year follow-up, while the percentage was 36.66% (n=33) at the 25-year follow-up and 28.33% (n=34) at the 15-year follow-up.

Hepatitis B or C was diagnosed in 73.46% (n=36) at the 35-year follow-up, while it was present in the 64.44% (n=58) at the 25-year follow-up and 49.16% (n=59) at the 15-year follow-up. There were no sex differences in either HIV (χ^2=0.808, p=0.668) or hepatitis B/C (χ^2=1.977, p=0.372) status at the 35-year follow-up.

Figure 2
Kaplan-Meier curve estimated for the heroin-dependent sample of patients against the curve that would be expected if the sample had been chosen randomly from the total Spanish population



Observed deaths (n)	Expected deaths (n)	Standardized mortality ratio	Upper 95% SMR-CI	Lower 95% SMR-CI	Log-rank test *p* value
146	12.43	11.75	9.95	13.77	$2 \cdot 10^{-16}$

Past and current use of heroin

The entire sample was using heroin at the start of the study. At the 25-year follow-up, the mean age of first heroin use was 18.39 (SD=2.995). Women started using heroin 1.77 years later than men (t-test=−2.008, p=0.049). There was no difference in mean age of first heroin use between the survivor and deceased samples (t-test=−1.185, p=0.241). Therefore, for the present study, we did not estimate the differences; the mean age of first use of heroin was the same as at the 25-year follow-up.

At the 35-year follow-up, 4.1% of survivors reported current heroin use, while 22.6% were using heroin at the 25-year follow-up and 39.7% at the 15-year follow-up. None of the female survivors were using heroin at the 35-year follow-up or at the 25-year follow-up compared with 5.3% of male survivors.

Current methadone maintenance therapy

The entire sample started MMT at the beginning of the study. At the 15-year follow-up, 60.4% of the survivors were still enrolled in MMT, whereas 39.6% were still enrolled at the 25-year follow-up, and 5.7% at the 35-year follow-up. There were no sex differences in current MMT enrollment in the survivor sample (Fisher's exact test, p=1), but it should be noted that only two of the survivors are currently enrolled in MMT.

Mortality

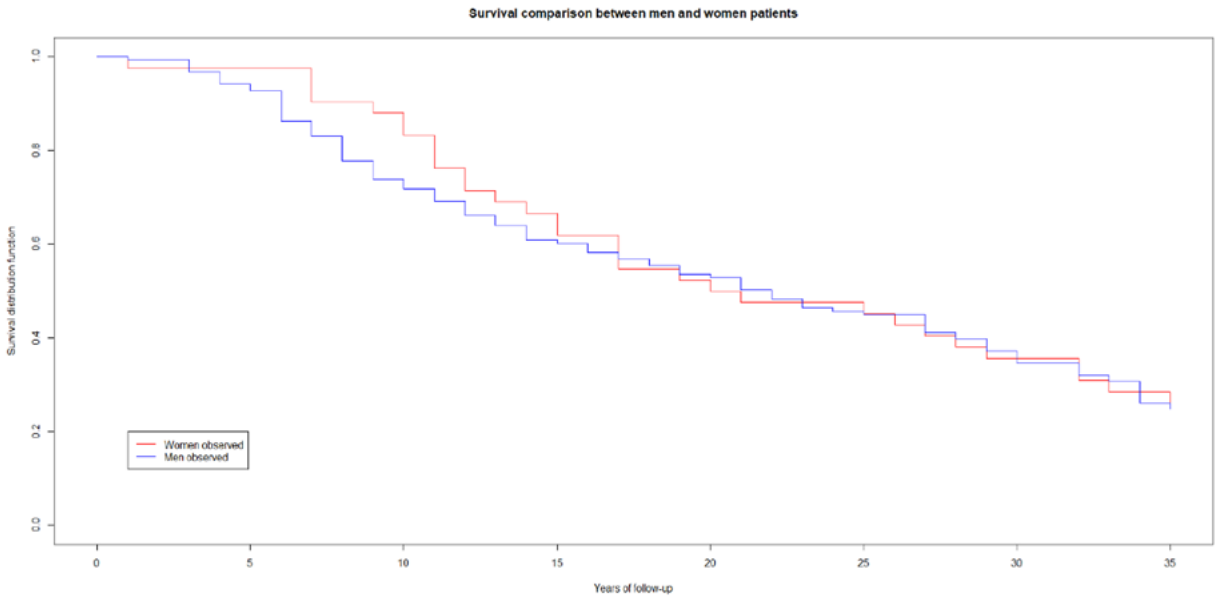
A total of 146 individuals (115 men, 31 women) had died by December 31, 2019. The first SMR calculations were performed using this sample size. The mean age of deceased patients was 42.68 years (SD=12.52); the youngest person died at the age of 22 and the oldest at the age of 93 years. There was no sex difference in mean age of death (t-test=0.530, p=0.601).

The expected death rate for the general population in the follow-up period analyzed was 12.43 in comparison with 146 deaths observed in the heroin-dependent population. Over the 35-year follow-up period, the SMR in the deceased group (n=146) was 11.75 (95% CI=9.95 – 13.77) (Fig. 2).

After repeating the analysis by sex, the results were as follows: 115 deaths were observed in the male heroin-dependent population in comparison to the expected death toll of 13.20 for the general population. Over the 35-year follow-up period, the SMR in the deceased group (n=115) was 8.71 (95% CI=7.22–10.44).

Thirty-one deaths were observed in the female heroin-dependent population in comparison to the expected death toll of 1.83 for the general population. Over the 35-year follow-up period, the SMR in the deceased group (n=31) was 16.94 (95% CI=11.71 – 23.75). There were no sex differences in Kaplan-Meier curves (p=0.070) (Fig. 3).

Figure 3
Kaplan-Meier curve estimated for the heroin-dependent sample of patients against the curve that would be expected if the sample had been chosen randomly from the total Spanish population



	Observed deaths (n)	Expected deaths (n)	Standardized mortality ratio	Upper 95% SMR-CI	Lower 95% SMR-CI	Log-rank test *p* value
Women	31	1.83	16.94	11.71	23.75	0.070
Men	115	13.2	8.71	7.22	10.42	

Table 3
Causes of death by sex since 15-year endpoint

	Men (n = 61)	Women (n = 16)	Total (N = 77)
Age (SD)	34.58 (8.43)	35.25 (4.69)	34.72 (7.77)
Cause of death [n (%)]			
HIV/AIDS	18 (29.5)	4 (25.0)	22 (28.6)
HCV/HBV/Cirrhosis	–	–	–
Overdose	6 (9.8)	–	6 (7.8)
Diseases*	1 (1.6)	–	1 (1.3)
Suicide	–	–	–
Accident	–	1 (6.3)	1 (1.3)
Homicide	1 (1.6)	–	1 (1.3)
Unknown	35 (57.4)	11 (68.8)	46 (59.7)

Note. *Diseases: Cancer, cerebrovascular event, respiratory disease.

Detailed information concerning cause of death was obtained for only 55 (37.67%) of these subjects using medical records and information provided by direct interview of relatives. Causes of death by sex are shown in Table 3 and Table 4. At the 15-year follow-up, the leading cause of death was HIV (28.6%), however, in the last 20 years, the leading causes of death were different diseases such as cancer, cerebrovascular events, or respiratory diseases (17.4%). However, statistical tests were not applied due to lack of data and excessive missing/unknown causes.

Risk factors associated with dying in the last 20 years

Logistic regression models were developed in order to identify risk factors associated with dying in the last 20 years (see Table 5 and Table 6). Excessive missing data made it difficult to identify these factors; therefore, we used only

Table 4
Causes of death by sex in the last 20 years

	Men (n = 54)	Women (n = 15)	Total (N = 69)
Age (SD)	50.84 (10.58)	49.53 (6.85)	50.55 (9.8)
Cause of death [n (%)]			
HIV/AIDS	3 (5.6)	1 (6.7)	4 (5.8)
HCV/HBV/Cirrhosis	3 (5.6)	–	3 (4.3)
Overdose	3 (5.6)	–	3 (4.3)
Diseases*	8 (14.8)	4 (26.7)	12 (17.4)
Suicide	1 (1.9)	–	1 (1.4)
Accident	–	–	–
Homicide	1 (1.9)	–	1 (1.4)
Unknown	35 (64.8)	10 (66.7)	45 (65.2)

*Note.**Diseases: Cancer, cerebrovascular event, respiratory disease.

Table 5
Deaths in the last 20 years and survivors

	Deaths (N = 69)	Survivors (N = 49)	Statistical test, *p*
Sex, male [n (%)]	54 (78.26)	38 (77.60)	.008[a], .927
HBV/HCV [n (%)]	35 (79.5)	36 (83.7)	8.771[a], .012
HIV+ [n (%)]	30 (71.4)	19 (46.3)	12.700[a], .002

Note. [a] Chi-square test.

Table 6
Variables associated with dying in the last 20 years

	β	SE	Wald	df	*p*	O.R.	95% CI
Death, Yes							
Intersection	-.134	.544	.060	1	.806	.875	
HIV+	1.089	.490	4.491	1	.026	2.972	1.138-7.765
HBV/HCV	-.687	.604	1.297	1	.255	.503	.154-1.642
Cox and Snell R2	.069						
Nagelkerke R2	.091						
Correct predictions	61.3%						

Table 7
Mortality in heroin-dependent population in follow-up studies

Study (year)	Country	Follow-up (years)	Deaths (%)	Sample size and derivation
Hser et al. (2001)	USA	33	48,9	581 white men admitted to the California Civil Addict Program
Nehkant et al. (2005)	UK	33	22	86 heroin dependents seen for therapeutic intervention
Jiménez-Treviño et al. (present study)	Spain	35	68,2	214 heroin dependents entering MMT for the first time
Stenbacka et al. (2010)	Sweden	37	50,4	1705 substance abusers identified through medical records
Fridell et al. (2019)	Sweden	42	42,3	1405 patients admitted to the unit for detoxification from narcotics

Note. MMT=methadone maintenance treatment.

clinical data such HIV+ and HBV/HCV infection. Our results show that HIV+ was associated with an increased risk of death in the last 20 years [OR = 2.972 (95% CI = 1.138-7.765)]. However, HBV/HCV infection was not significant in predicting these deaths.

Discussion

We present the third wave of the follow-up on a sample of 214 heroin-dependent patients consecutively enrolled in MMT between 1982 and 1984 in the Asturias Public Health Service, 35 years after first entering MMT. Previous reports by our group show data at the 15- and 25-year endpoints (Jimenez et al., 2000; Jimenez et al., 2011).

To our knowledge, including ours, there are only 5 published studies of heroin-dependent patients with more than 30 years' follow-up, all in Western countries (see Table 7).

In this third wave, we were able to locate 91.1% of the original sample. This attrition rate of under 10% is similar to the other long-term follow-up studies (Fridell et al., 2019; Hser et al., 2001; Nehkant, Rathod, Addenbrooke & Rosenbach, 2005) and constitutes an improvement compared to our attrition rates at 15 years (63.6%) and 25 years (25.7%). The main reason for the increase in our location rate is the progressive transition to electronic health and death records in Spain. Electronic health records (EHRs) have emerged largely as a mean to improve health-care quality and to capture billing data, but they may potentially be used to facilitate data collection or conduct entirely EHR-based observational studies (Cowie et al., 2017).

Our study confirms the high long-term mortality of heroin addicts, even after enrollment in MMT. Our death rate of 68.2% after 35 years is the highest among the long-term follow-up studies but agrees with a number of studies in non-MMT patients with an annual death rate of around 2% per year in young adult drug abusers (Haastrup & Jepsen, 1988; Oppenheimer, Tobutt, Taylor & Andrew, 1994; Ravndal & Vaglum, 1998; Segest, Mygind & Bay, 1990), suggesting a failure of long-term death prevention in MMT programs. It should be noted that it is difficult to compare these types of studies: there are differences in MMT programs (access, duration, inclusion criteria, etc.) between countries and within the same country, they use different study groups, methods, and calculations as well as different sample sizes, countries of origin, and length of follow-up periods.

We have used the SMR as a more accurate way to compare death figures. After a mean follow-up period of 35 years, the SMR of 11.75 (8.71 men vs. 16.94 women) in our cohort was higher than the 6.68 men vs. 4.98 women found by Fridell et al. (2019) and the 3.3 men vs. 3.5 women found by Stenbacka, Leifman & Romelsjö (2010), but there is a significant decrease compared with the 22.51 SMR we found at the 25-year endpoint (Jimenez et al., 2011).

The reason for this drop in the SMR may be found in the low rates of opiate use in our sample for the last 10 years (only 5% of the males and none of the females reported current heroin use at the 35-year endpoint), as well as the universal availability of an effective HCV treatment in Spain in the past decade (Berenguer, 2018). In fact, despite a near 70% prevalence of HBV/HCV infection in our sample, it is not one of the variables associated with dying in the last 20 years. Cirrhosis of the liver remained among the top 5 causes of death in the 37-year follow-up study by Stenbacka et al. (2010). Nehkant et al. (2005) also reported that liver disease was frequently mentioned on the death certificates in their study, highlighting the need for regular liver function screening for early detection and treatment. Unfortunately, our lack of data on causes of death in our sample prevents us from confirming this statement. Based on Spanish population studies, elimination of HCV infection would have decreased HCV-related deaths by 20% (Buti et al., 2017). The impact of HCV on mortality has been already highlighted in studies on the HIV population: having an HCV co-infection with AIDS yielded an SMR of 20.8 (16.5-26.1) in HIV+ subjects followed-up for the period from 1997 - 2008 in the Cohorts of Spanish Network on HIV/AIDS (Hernando et al., 2012).

While numerous studies have demonstrated the effectiveness of MMT for reducing morbidity, risk of HIV infection, and mortality (Kleber, 2008), our HBV/HCV and HIV rates of 70% and 45% respectively, as well as our mortality rate of 68.2% in MMT patients, seem to reflect poor effectiveness. Unfortunately, we do not have a control sample of non-MMT heroin addicts for comparison, but our rates of HIV and HBV/HCV are higher than those published in previous long-term follow-up studies: 30.7% of HIV infection rate in Bauer et al. (2008) 10-year sample or 41.7% and 48% of HBV/HCV infection rate in Hser et al. (2001) and Fridell et al. (2019) studies. It is important to point out that most of the HCB/HCV and HIV cases were diagnosed in the first 15 years of follow-up. Only 18% of the HBV/HCV and 29% of the HIV cases were diagnosed in the last 20 years of follow-up.

On the other hand, the rate of current heroin use in our survivor sample (5.26% men/0% women) is lower than previous reports in long-term follow-up studies of heroin addicts such as the ones by Hser et al. (2001) (20.7% after 33 years), Nehkant et al. (2005) (20% after 33 years), and Nyhlén, Fridell, Bäckström, Hesse & Krantz (2011) (27% after 37 years). It is encouraging that trend studies find that the proportion of patients still addicted is declining, despite the pessimistic views expressed two decades ago by Hser et al. (2001). However, there is no way of knowing whether the proportion of drug-related deaths reflects selection bias. The 35-year follow-up survivors may represent the patients in the initial sample with the least severe dependency and thus more likely to stop using heroin.

Taken together these results, they may explain our higher mortality rate and lower current heroin use, as previous follow-up studies in Spanish, Swiss and Scandinavian populations have showed that HIV-related deaths are the most prevalent in MMT patient cohorts (Davstad, Stenbacka, Leifman, & Romelsjö, 2009; Rehm et al., 2005; Sánchez-Carbonell & Seus, 2000; Stenbacka et al., 2010). Even after the implementation of antiretroviral treatments, HIV infection is still associated with increased mortality among heroin users as heroin dependence also compromise effective HIV treatment by influencing both access and adherence to antiretroviral therapy. Exposure to addictive substances may also have direct immunosuppressive effects independent of their impact on access and adherence to treatment (Sammet, Walley & Bridden, 2007).

Moreover, Hepatitis B and HIV increased infection rates are also associated with severity of the addiction and duration of injecting drug use (Levine et al., 1995; Sammet, Walley & Bridden, 2007) and this may be the cause of our low rates of actual heroin use in our sample, as most of the heavy users would have died due to a higher risk of death, not only by overdose but also because of the greater prevalence of these medical conditions.

As a brief conclusion to these results, we may safely say that, 35 years after seeking methadone treatment for heroin dependence, either you have quit or you are dead.

Limitations of the study have already been covered in the Discussion. The main limitations of the study include the large amount of missing data on causes of death as well as the lack of an untreated control sample. Other limitations include the lack of data on HIV and HBV status at the start of the follow-up period and the lack of standardization of the ad hoc protocol that was used.

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Conflict of interests

The authors declare that there is no conflict of interest. The funding sources had no involvement in this study.

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