Development of Statistical Methodology to Study the Incidence of Drug Use

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DEVELOPMENT OF STATISTICAL METHODOLOGY TO STUDY THE INCIDENCE OF DRUG USE

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https://sites.google.com/site/asanchezniubo

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to Núria, Lluc and Arnau

Preface

This work aims to contribute methodologically in the epidemiology of drug use, particularly estimation of incidence. No incidence figures of drug use in Spain had ever been published, prior to those appearing in these articles, and relatively little has been published for other countries.

Since around 2000, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), which is an agency of the European Union, has been making a concerted effort to promote the determination and publication of drug use incidence figures, given their great importance in designing prevention policies. The approaches used and results obtained by our research have been presented in three EMCDDA meetings (years 2007, 2008 and 2012), at a monographic meeting on incidence promoted by the Norwegian Institute for Alcohol and Drug Research (SIRUS) in 2009, and in the framework of a European project on new methodological tools for policy and programme evaluation (JUST/2010/DPIP/AG/1410) which ran from 2010 to 2012.

This work therefore contributes not only by presenting drug use incidence results for Spain, but also by describing the development of methods and sharing ideas that may be adapted for use in other countries.

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Justament fa 10 anys que vaig entrar a l'IMIM com a simple diplomat, i recordo lo primer que em va preguntar en Jordi Alonso: *"Escolta, tu voldràs fer algun dia la tesi o què?"*. Doncs aquí estic, complint la meva paraula. A més d'en Jordi, he tingut meravellosos companys sense excepció i voldria agrair tot el vostre suport: Sali, Sandra, Puri, Moma, Josu, Gemma, Miki, Olatz, Àngels, Eli, Montse F., Dave (no sé què faria sense tu amb l'anglès), Toni, Chus, Diego, Mendi, Ester,

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Voldria donar les gràcies a tots aquells que m'han animat a acabar la tesi: als meus companys d'escacs perquè tornés a jugar els campionats; a la Marina, la Laura i la Rakel, qui les dec moltes hores de guarderia; al David Mata per creure més en mi que jo mateix; a tots els col·legues de Linyola amb els que he compartit tantes experiències; i als esparreguerins per la seva càlida convivència.

Finalment, vull dedicar aquesta tesi a la meva família, sobretot als meus pares, seguidors incondicionals dels meus (insignificants) èxits; als meus sogres per totes les hores i habitacions aïllades que m'han facilitat; als meus cunyats/des, en especial a Vicent qui ha escoltat els meus desassossecs amb la tesi; i per damunt de tot i tothom, als qui fan que la meva vida tingui un sentit: la Núria, en Lluc i l'Arnau.

Gràcies / Gracias / Thank you / Grazie / Takk

May the dice be with us,

Albert

September 2013

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Abstract

In the epidemiology of drug use, where by drugs we mean illicit psychoactive substances, incidence refers to the number of individuals who make their first use during a specified period of time. This epidemiological measure is important because it indicates the time trend of the spread of drug users in the population and for this reason is important in the design of prevention policies.

In Spain, the prevalence of heroin use was high in the 80's and 90's, creating social alarm; currently, the prevalences of cocaine and cannabis are among the highest in Europe. However, to date incidence has not been estimated in Spain, and relatively little has been done in other countries.

Since drug users constitute a hidden population, more complex approaches are required in order to obtain incidence figures. Prior to this study two methods were available for estimating incidence from records of detoxification treatments: the "lag-correction" and "back-calculation" methods. Both methods are based on firstly obtaining a distribution for the lapse of time ("lag time") between an individual's first drug use and his/her first admission to treatment. The difference between the methods is mainly that the "lag-correction" method requires individual information about drug use and only corrects for those individuals admitted to their first treatment at some point in time later than the period observed; and the "back-calculation" method only needs aggregated data from treatment registers and an external lag time distribution. On the other hand, a third method based on periodic

general population surveys is the "composite retrospective estimator" which is based on a joint, or composite, estimation of the incidence combining reports about the first drug use of individuals interviewed in the surveys.

In the context of Spain and in relation to the type of data accessible, application of the above methods entailed a number of limitations. Therefore, we proposed to adapt and develop new methods for estimating incidence of heroin, cocaine and cannabis use, separately, in Spain since the 70's.

This work consists of the following articles published in international peer-reviewed journals:

- **Problematic heroin use incidence trends in Spain**. Sanchez-Niubo A, Fortiana J, Barrio G, Suelves JM, Correa JF, Domingo-Salvany A. Addiction 2009; 104(2): 248-255.
- **A multi-state model to estimate incidence of heroin use**. Sanchez-Niubo A, Aalen OO, Domingo-Salvany A, Amundsen EJ, Fortiana J, Røysland K. BMC Med Res Methodol 2013; 13(1):4.
- **Incidence trends of cannabis and cocaine use from periodic Spanish general population surveys: effect of standardising results by age structure**. Sanchez-Niubo A, Sordo L, Fortiana J, Brugal MT, Domingo-Salvany A. Addiction 2013; 108(8): 1450-1458.

The first article dealt with estimation of heroin use incidence in Spain from 1971 to 2005 using treatment data available for the period 1991 to 2005. The expected values of a frequency table tabulated between the years of first drug use (35 rows: 1971-2005) and the lag time in years between first use and first treatment (35 columns: 0-34) were estimated by fitting a log-linear model of quasi-independence. This table was initially incomplete due to two inherent truncations to the sources

of information: right truncation affecting those individuals admitted to their first treatment at some point in time later than the period observed and left truncation affecting those individuals who entered their first treatment before the observed period of time. The estimated incidences were the row marginals of expected frequencies and the estimation of the lag time distribution resulted from the column parameter estimates of the model. The estimated incidences were highest around 1980 and declined steadily until 2000, followed by a period of relative stability until 2005. Lag times between first drug use and first treatment had a median of 3 years. This model assumed independence between rows and columns, equivalent to that lag times were equidistributed for any year of first heroin use. However, we know that treatment offer was not stable over the years. Therefore, although incidence estimates were considered to agree approximately with the known characteristics of the epidemic in Spain, we considered that it was not appropriate to rely on the assumption of independence.

The second article dealt with estimating the incidence of heroin use in Spain, this time from 1971 to 2006, using the same treatment data as in the previous article, and also incorporating information about mortality rates related to heroin use and permanent cessation rates of consumption. A multi-state model was designed, where the initial state "heroin use" was followed by a transition to either "first treatment" or to "left heroin use" (permanent cessation or death). Incidence was considered as immigration to the initial state. The observed number of people who consumed heroin for the first time and who entered their first treatment in two particular years, was modeled as a Poisson variable whose expected means took into account transitions between the three states. The probability of a given heroin user entering their first treatment at a particular instant was assumed independent of the time when they first consumed heroin. Due to several assumptions about the parameters of first treatment, cessation and death, we performed a sensitivity analysis to compare differences in the estimates. The fit was considered

adequate but estimates for the last few years were progressively more unstable, possibly due to the low number of heroin users observed. The highest estimated incidences were between 1985 and 1990 with a steady decline until 2005. The trends in the estimated incidences for years prior to 2000 were considered to agree better with characteristics of the heroin epidemic in Spain than those from the first article.

The third paper dealt with estimating the incidence of cocaine and cannabis in Spain from 1971 to 2008 using data from eight biennial general population surveys conducted between 1995 to 2009. The method was the same as the "composite retrospective estimator" but incorporating standardization of incidence by the age structure of the population because this had changed over the years. The estimated "raw" incidences (not standardized) were valid for every year but not for the assessment of trends needed to design prevention strategies. The standardized incidence estimates were the most suitable for representing the trends, since they reliably indicate the direction of the epidemic. In general, incidence of cocaine and cannabis use tended to rise until 2000 and stabilized afterwards. These trends were consistent with the known epidemic in Spain.

To assess the suitability of the different methods, incidences were estimated for each drug using each method, whenever possible. In general terms the conclusions were that:

- The multi-state model seemed the most appropriate to estimate incidences of heroin use in Spain in the years prior to 2000. However, for more recent years we considered some method supported by a proper lag time distribution more reliable, such as the log-linear model.
- To estimate incidences of cocaine and cannabis use in Spain, we considered that the composite retrospective estimator, based on general population surveys, and applying standardization for the

population age structure, provided more accurate estimates to assess incidence trends than those from methods based on treatment data.

The incidence trends estimated for the consumption of each drug agreed with their known epidemic characteristics and therefore, may be of value to health policy makers. However, these estimates can not be usually calculated until from 2 to 5 years after data collection, this being a limitation to their use in prevention strategies and health policy evaluation. Therefore, a proposal for future lines of research would be to study dynamic models that describe the drug user's career. This class of models can predict trends through analysis of different scenarios and permit making short-term predictions.

Resum

En l'epidemiologia de consum de drogues, entenent-se com drogues les substàncies psicoactives i il·lícites, la incidència es refereix al nombre d'individus que realitzen el seu primer consum durant un temps determinat. Aquesta mesura epidemiològica és important perquè indica la tendència de la propagació en el temps del nombre de consumidors de drogues en la població i per això la seva importància en el disseny de polítiques de prevenció.

A Espanya, les prevalences de consum d'heroïna van ser molt elevades en els anys 80 i 90 creant una alarma social i, actualment, les prevalences en cocaïna i cànnabis són de les més elevades d'Europa. No obstant això, fins ara a Espanya no hi han hagut estimacions d'incidència, i relativament poc s'ha fet en altres països.

Atès que els consumidors de drogues constitueixen una població oculta, calen enfocaments més complexos amb la finalitat d'obtenir xifres d'incidència. Abans del present treball existien dos mètodes per estimar incidència a partir de registres de tractaments sobre desintoxicació: els mètodes "lag-correction" i "back-calculation". Ambdós mètodes es basen en obtenir primer una distribució del lapse de temps ("lag time") entre el primer consum d'un individu i la primera vegada que entra a un tractament. La diferència d'aquests dos mètodes és principalment que el "lag-correction" requereix informació individual de cada consumidor i que corregeix només la incidència per a aquells individus que realitzen el seu primer tractament després de finalitzat

el període de temps d'observació, i el "back-calculation" només necessita dades agregades de tractament i una distribució del "lag time" externa a les dades. D'altra banda, un tercer mètode basat en enquestes periòdiques a població general és l'"estimador retrospectiu compost" que es basa en una estimació conjunta de la incidència combinant els informes de primer consum dels individus entrevistats en aquestes enquestes.

En el context d'Espanya i en relació al tipus de dades als quals es pot accedir, es va veure que l'aplicació dels métodes anteriors patia d'una sèrie de limitacions. Per tant, es va proposar adaptar i desenvolupar nous mètodes per a l'estimació de la incidència de consum d'heroïna, cocaïna i cànnabis, per separat, a Espanya des dels anys 70.

Aquest treball es composa dels següents articles publicats en revistes internacionals amb revisió per parells:

- **Problematic heroin use incidence trends in Spain**. Sanchez-Niubo A, Fortiana J, Barrio G, Suelves JM, Correa JF, Domingo-Salvany A. Addiction 2009; 104(2): 248-255.
- **A multi-state model to estimate incidence of heroin use**. Sanchez-Niubo A, Aalen OO, Domingo-Salvany A, Amundsen EJ, Fortiana J, Røysland K. BMC Med Res Methodol 2013; 13(1):4.
- **Incidence trends of cannabis and cocaine use from periodic Spanish general population surveys: effect of standardising results by age structure**. Sanchez-Niubo A, Sordo L, Fortiana J, Brugal MT, Domingo-Salvany A. Addiction 2013; 108(8): 1450-1458..

En el primer article es va proposar estimar la incidència de consum d'heroïna a Espanya des de 1971 fins 2005 a partir de dades de tractament disponibles entre 1991 i 2005. Per això primer es van estimar els

valors esperats d'una taula de freqüències tabulada entre els anys d'inici de consum (35 files: 1971-2005) i el lapse de temps en anys entre el primer consum i primer tractament (35 columnes: 0-34), ajustant-la a un model log-lineal de quasi-independència. Aquesta taula estava incompleta a causa de dos truncaments inherents a la font d'informació: el truncament dret que afecta a aquells individus que realitzen el seu primer tractament després de finalitzat el període de temps d'observació i el truncament esquerre que afecta a aquells individus que van realitzar un primer tractament abans del període d'observació. La incidència estimada va ser la marginal de les files de freqüències esperades i l'estimació de la distribució del lapse de temps va resultar de les estimacions dels paràmetres columna del model. Les incidències estimades més altes van ser al voltant de l'any 1980 i van disminuir sense pausa fins a l'any 2000 amb una lleu estabilització fins al 2005. El lapse de temps entre el primer consum i primer tractament va tenir una mediana de 3 anys. Per a aquest model es va suposar independència entre files i columnes, el que equival a suposar que els lapses de temps són equidistribuits per a qualsevol any de primer consum d'heroïna. En canvi, l'oferta de tractament no va ser estable al llarg dels anys. Per tant, tot i que es va considerar que les estimacions d'incidència concordaven aproximadament amb l'epidèmia coneguda a Espanya, no és convenient recolzar-se amb la hipòtesi d'independència.

En el segon article es va proposar estimar la incidència de consum d'heroïna a Espanya, ara des de 1971 fins 2006 a partir de dades de tractament com en l'anterior article, i incorporant informació de taxes de mortalitat relacionada amb el consum d'heroïna i de cessament permanent de consum. Es va construir un model de múltiples estats, on l'estat inicial "consumir heroïna" va ser seguit d'una transició a l'estat d'"entrar a primer tractament" o l'estat d'"abandonament del consum" (cessament permanent o mort). La incidència es va considerar com el nombre d'individus que entraven a l'estat inicial. El nombre observat de persones que van realitzar el seu primer consum i van entrar al

primer tractament en dos anys determinats va ser modelat com una variable de Poisson, on els termes esperats mitjos tenien en compte les transicions entre els tres estats. Es va assumir que la probabilitat que un consumidor d'heroïna entrés a primer tractament en un moment donat era independent de l'instant en què aquest individu va fer el seu primer consum d'heroïna. A causa de diverses suposicions en els paràmetres de primer tractament, cessament i mort, es va realitzar una anàlisi de sensibilitat per contrastar diferències en les estimacions. L'ajust es va considerar adequat però les estimacions en els últims anys van ser progressivament més inestables, possiblement a causa del baix nombre observat de consumidors d'heroïna. Les incidències estimades més altes es van situar entre 1985 i 1990 amb un descens progressiu fins al 2005. Les tendències de les incidències estimades en anys previs al 2000 es van considerar més acords a l'epidèmia d'heroïna a Espanya que la del primer article.

En el tercer article es va proposar estimar la incidència de consum de cocaïna i cànnabis a Espanya des de 1971 fins 2008 a partir de dades de vuit enquestes biennals a població general des de l'any 1995 al 2009. El mètode va ser el mateix que l'"estimador retrospectiu compost" però incorporant l'estandardització de la incidència per l'estructura d'edat de la població a causa que aquesta havia canviat al llarg dels anys. Les incidències estimades crues (sense estandaritzar) van ser vàlides per a cada any però no per valorar la seva tendència per a dissenyar estratègies de prevenció. Les incidències estimades estandaritzades van ser més adequades per representar les tendències ja que indiquen més fiablement la direcció de l'epidèmia. En general, les tendències d'incidències en el consum de cocaïna i cànnabis van ser creixents i a partir del 2000 es van estabilitzar. Aquestes tendències van concordar amb l'epidèmia coneguda a Espanya.

Per valorar la idoneïtat dels diferents mètodes es van estimar les incidències de consum de cada droga amb cada mètode sempre que fos

possible. En línies generals es va concloure el següent:

- El model multi-estat sembla ser el més apropiat per estimar incidències de consum d'heroïna a Espanya en els anys previs al 2000. En canvi, per anys més recents considerem més fiable algun mètode basat en una distribució adequada del lapse de temps, com el model log-lineal.
- A les incidències estimades de consum de cocaïna i cànnabis a Espanya, considerem que l'estimador retrospectiu compost, al basar-se en dades d'enquestes a població general, i aplicant l'estandardització per l'estructura d'edat poblacional, proporciona estimacions més encertades per valorar les tendències d'incidència que els mètodes basats en dades de tractament.

Les tendències d'incidència estimades per al consum de cada droga concorden amb les seves epidèmies conegudes i per tant poden ser valorades pels responsables de polítiques de salut. No obstant això, aquestes estimacions no poden ser habitualment calculades fins de 2 a 5 anys després de la recollida de dades, sent una limitació per a la prevenció i avaluació de polítiques de salut. Per tant, com a futures línies de recerca es proposa estudiar models dinàmics que descriguin la carrera d'un consumidor de drogues. Aquesta classe de models pot predir tendències mitjançant l'anàlisi de diferents escenaris i fer prediccions a curt termini.

Resumen

En la epidemiología de consumo de drogas, entendiéndose como drogas las sustancias psicoactivas e ilícitas, la incidencia se refiere al número de individuos que realizan su primer consumo durante un tiempo determinado. Esta medida epidemiológica es importante porque indica la tendencia de la propagación en el tiempo del número de consumidores de drogas en la población y por ello su importancia en el diseño de políticas de prevención.

En España, las prevalencias de consumo de heroína fueron muy elevadas en los años 80 y 90 creando una alarma social y, actualmente, las prevalencias en cocaína y cannabis son de las más elevadas de Europa. Sin embargo, hasta la fecha en España no han habido estimaciones de incidencia, y relativamente poco se ha hecho en otros países.

Dado que los consumidores de drogas constituyen una población oculta, se necesitan enfoques más complejos con el fin de obtener cifras de incidencia. Antes del presente trabajo existían dos métodos para estimar incidencia a partir de registros de tratamientos sobre desintoxicación: los métodos "lag-correction" y "back-calculation". Ambos métodos se basan en obtener primero una distribución del lapso de tiempo ("lag time") entre el primer consumo de un individuo y la primera vez que entra a un tratamiento. La diferencia de estos dos métodos es principalmente que el "lag-correction" requiere información individual de cada consumidor y que corrige sólo la incidencia para aquellos individuos que realizan su primer tratamiento después de finalizado el

período de tiempo de observación, y el "back-calculation" sólo necesita datos agregados de tratamiento y una distribución del "lag time" externa a los datos. Por otro lado, un tercer método basado en encuestas periódicas a población general es el "estimador retrospectivo compuesto" que se basa en una estimación conjunta de la incidencia combinando las informaciones de primer consumo de los individuos entrevistados en dichas encuestas.

En el contexto de España y en relación al tipo de datos a los que se puede acceder, se vio que la aplicación de los métodos anteriores adolecía de una serie de limitaciones. Por tanto, se propuso adaptar y desarrollar nuevos métodos para la estimación de la incidencia de consumo de heroína, cocaína y cannabis, por separado, en España desde los años 70.

Este trabajo se compone de los siguientes artículos publicados en revistas internacionales con revisión por pares:

- **Problematic heroin use incidence trends in Spain**. Sanchez-Niubo A, Fortiana J, Barrio G, Suelves JM, Correa JF, Domingo-Salvany A. Addiction 2009; 104(2): 248-255.
- **A multi-state model to estimate incidence of heroin use**. Sanchez-Niubo A, Aalen OO, Domingo-Salvany A, Amundsen EJ, Fortiana J, Røysland K. BMC Med Res Methodol 2013; 13(1):4.
- **Incidence trends of cannabis and cocaine use from periodic Spanish general population surveys: effect of standardising results by age structure**. Sanchez-Niubo A, Sordo L, Fortiana J, Brugal MT, Domingo-Salvany A. Addiction 2013; 108(8): 1450-1458.

En el primer artículo se propuso estimar la incidencia de consumo de heroína en España desde 1971 hasta 2005 a partir de datos de tratamiento disponibles entre 1991 y 2005. Para ello primero se estimaron

los valores esperados de una tabla de frecuencias tabulada entre los años de inicio de consumo (35 filas: 1971-2005) y el lapso de tiempo en años entre el primer consumo y primer tratamiento (35 columnas: 0-34), ajustándola a un modelo log-lineal de casi-independencia. Dicha tabla estaba incompleta debido a dos truncamientos inherentes a la fuente de información: el truncamiento derecho que afecta a aquellos individuos que realizan su primer tratamiento después de finalizado el período de tiempo de observación, y el truncamiento izquierdo que afecta a aquellos individuos que realizaron un primer tratamiento antes del período de observación. La incidencia estimada fue la marginal de las filas de frecuencias esperadas y la estimación de la distribución del lapso de tiempo resultó de las estimaciones de los parámetros columna del modelo. Las incidencias estimadas más altas fueron alrededor del año 1980 y fue descendiendo sin pausa hasta el año 2000 con una leve estabilización hasta el 2005. El lapso de tiempo entre el primer consumo y primer tratamiento tuvo una mediana de 3 años. Para este modelo se supuso independencia entre filas y columnas, lo que equivale a suponer que los lapsos de tiempo son equidistribuidos para cualquier año de primer consumo de heroína. En cambio, la oferta de tratamiento no fue estable a lo largo de los años. Por tanto, aunque se consideró que las estimaciones de incidencia concordaban aproximadamente con la epidemia conocida en España, no es conveniente apoyarse con la hipótesis de independencia.

En el segundo artículo se propuso estimar la incidencia de consumo de heroína en España desde 1971 hasta 2006 a partir de datos de tratamiento como en el anterior artículo pero hasta 2006, y además incorporando información de tasas de mortalidad relacionada con el consumo de heroína y de cese permanente de consumo. Se construyó un modelo de múltiples estados, donde el estado inicial "consumir heroína" fue seguido de una transición al estado de "entrar a primer tratamiento" o al estado de "abandono del consumo" (cese permanente o muerte). La incidencia se consideró como el número de individuos que entraban

al estado inicial. El número observado de personas que realizaron su primer consumo y entraron al primer tratamiento en dos años determinados, fue modelado como una variable de Poisson cuyos promedios esperados tenían en cuenta las transiciones entre los tres estados. Se asumió que la probabilidad de que un consumidor de heroína entrara a primer tratamiento en un momento dado era independiente del instante en que este individuo hizo su primer consumo de heroína. Debido a varias suposiciones en los parámetros de primer tratamiento, cese y muerte, se realizó un análisis de sensibilidad para contrastar diferencias en las estimaciones. El ajuste se consideró adecuado pero las estimaciones en los últimos años fueron progresivamente más inestables, posiblemente debido al bajo número observado de consumidores de heroína. Las incidencias estimadas más altas se situaron entre 1985 y 1990 con un descenso progresivo hasta el 2005. Las tendencias de las incidencias estimadas en años previos al 2000 se consideraron más acordes a la epidemia de heroína en España que la del primer artículo.

En el tercer artículo se propuso estimar la incidencia de consumo de cocaína y cannabis en España desde 1971 hasta 2008 a partir de datos de ocho encuestas bienales a población general desde el año 1995 al 2009. El método fue el mismo que el "estimador retrospectivo compuesto" pero incorporando la estandarización de la incidencia por la estructura de edad de la población debido a que esta había cambiado a lo largo de los años. Las incidencias estimadas crudas (sin estandarizar) fueron válidas para cada año pero no para valorar su tendencia en cuánto a diseñar estrategias de prevención. Las incidencias estimadas estandarizadas fueron más adecuadas para representar las tendencias ya que indican más fiablemente la dirección de la epidemia. En general, las tendencias de incidencias en el consumo de cocaína y cannabis fueron crecientes y a partir del 2000 se estabilizaron. Estas tendencias fueron acordes con la epidemia conocida en España.

Para valorar la idoneidad de los diferentes métodos se estimaron las incidencias de consumo de cada droga con cada método siempre que fuese posible. En lineas generales se concluyó lo siguiente:

- El modelo multi-estado parece ser el más apropiado para estimar incidencias de consumo de heroína en España en los años previos al 2000. En cambio, para años más recientes consideramos más fiable algún método basado en una distribución adecuada del lapso de tiempo, como el modelo log-lineal.
- En las incidencias estimadas de consumo de cocaína y cannabis en España, consideramos que el estimador retrospectivo compuesto, al basarse en datos de encuestas a población general, y aplicando estandarización por la estructura de edad poblacional, proporciona estimaciones más acertadas para valorar tendencias de incidencias que los métodos basados en datos de tratamiento.

Las tendencias de incidencia estimadas para el consumo de cada droga son acordes a sus epidemias conocidas y por tanto pueden ser valoradas por los responsables de políticas de salud. Sin embargo, estas estimaciones no pueden ser habitualmente calculadas hasta 2 y 5 años después de la recogida de datos, siendo una limitación para la prevención y evaluación de políticas de salud. Por tanto, como futuras lineas de investigación se propone estudiar modelos dinámicos que describan la carrera de un consumidor de drogas. Esta clase de modelos puede predecir tendencias por medio de análisis de diferentes escenarios y hacer predicciones a corto plazo.

Part I

Introduction

The "junkie" lifestyle has seduced a whole generation, taking the lives of many in something which, without exaggeration, may be considered a gradual, silent holocaust.

Juan F. Gamella

CHAPTER

1

Context

The term "incidence of drug use" needs to be defined clearly in the context of the present work, since it can have various interpretations. Moreover, as the setting is Spain, a brief history of Spanish epidemiology of drug use and data collection systems will be presented, along with a comparison between the current state of drug consumption in Spain and abroad. Given the context, the study of drug use incidence in Spain deserves to be justified.

1.1 Epidemiology of drug use

An important goal for epidemiological research on drug use is to quantify the rates of new occurrences (*incidence*) and the total extent of cases (*prevalence*) within a specified period of time in human populations[1]. Thus, *incidence* and *prevalence* are the main concepts employed in epidemiological research to understand the spread and magnitude of a disease, whether infectious, addictive, or otherwise.

Regarding *drug use*, this expression needs to be clarified. In the first place, *drugs* may be used colloquially to refer to medicinal drugs or other psychoactive substances that anyone can purchase legally, as well as to illicit substances.

Whereas consumption of legal substances like tobacco or alcohol has been extensively studied, that of illicit ones like heroin or cannabis has the particularity that consumers naturally fear disclosure of their behaviour. Such consumption therefore tends to be hidden, and obtaining information about it can be difficult. Without any desire to provoke controversy, it seems generally accepted that a moderate ingestion of certain kinds of illicit drugs is considered harmless, and possibly even beneficial. In contrast it is generally considered undeniable that abuse of these drugs eventually becomes problematic. The problem is how to define the threshold beyond which moderate use can be expected to become problematic. Several diagnostic procedures are available to assess whether a person has a *drug use problem*. To date, the most widely used is that appearing in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). It contemplates two diagnoses: substance abuse and substance dependence. If a person has one of these diagnoses we consider them to have a *drug use disorder*. A new version, the DSM-V, expected to be published shortly, replaces these two diagnoses with a new one, "addictions and related disorders", based on a more quantitative approach to the assessment of severity. Apart from the DSM-IV and V, various other questionnaire-based screening instruments are also available to facilitate detection, and consequently for prevention of drug problems, some specifically tailored for addictions, such as the Drug Abuse Screening Test (DAST-20), Severity Dependence Scale (SDS), or others more focused on a specific substance, like the Cannabis Abuse Screening Test (CAST) [2].

It seems practically certain, as mentioned above, that a very frequent consumption of a drug will lead, sooner or later, to problematic use. This hidden activity or behaviour would normally have far-reaching consequences for most persons who continue consuming beyond an initial experimentation phase. The use of one particular type of drug is often followed by the use of other drugs which entail greater risks of addiction and adverse consequences, such as overdose, HIV, hepatitis C, death, etc. Therefore, resources dedicated to prevention would be more efficiently used if applied to reducing recruitment rates (incidence) than to other posterior measures like treatment, harm reduction and social reintegration. However, we must also accept that initiation of drug use does not necessarily imply a subsequent

habitual use. The question is: why is the study of incidence of experimental and occasional use so important? One answer could be that it can help to elucidate the path leading from occasional to problematic use. But even more important is the issue of who contributes to "spreading" drug use. An individual who is susceptible to consume some illicit drug is unlikely to be convinced to do so by a *junkie*, by which we mean a person with physical and/or psychological signs of problematic drug use. In contrast, a non-problematic user is more likely to be *evangelical* about drug use, trying to spread this behaviour to other susceptible persons. As non-problematic use will probably only be experimental or occasional, attempts to determine incidence should focus on including individuals who have used the drug/s in question at least once in their life.

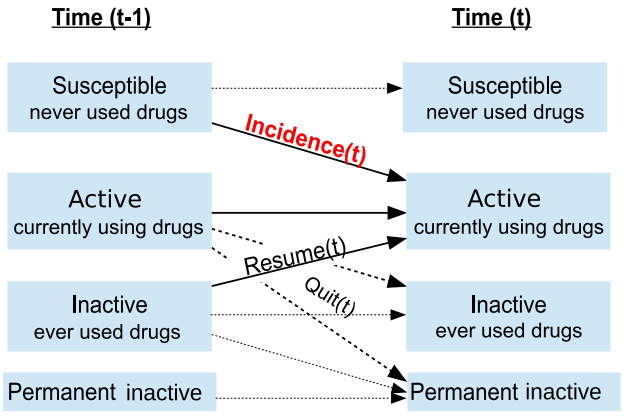

Figure 1.1: Potential drug user's transitions between two units of time.

Figure 1.1 shows how epidemiological measures, determined for two different time periods, are related. At time $t-1$ we have: susceptible individuals who have never used drugs, currently active drug users, currently inactive drug users, and people who from $t-1$ onwards will never use drugs (in most part because of death). The number of drug users in the population at time t (prevalence P_t), is given by[3]:

$$P_t = P_{t-1} + I_t - Q_t + R_t,$$

where P_{t-1} is the number of people who were active users at any time in period $t-1$, I_t is the number of people who start using drugs (incidence) at any time between the end of period $t-1$ and start of t, Q_t is the number of drug users who quit their use before the beginning of period t, and R_t is the number of people who had been active drug users at some previous time, before the start of period $t-1$ and resume their use during period t. Therefore, incidence represents the process of the spread of drug use, i.e. the appearance of new drug users, in the population.

Although incidence of drug use has just been defined as an incidence of first use ever, it could have other definitions such as "first continuous use" or "entry into a period of (continuous) drug use" (whether new or not). Nevertheless, apart from the fact that drug users may more easily remember their first use, incidence of first use is a suitable measure of the tendency of new individuals to become involved in the problem[3]. Incidence figures provide an indication of trends in the spread of drug use, and in particular help in ascertaining whether the number of drug users is rising (epidemic phase), falling, or has stabilised (endemic phase)[4].

Summing up, in the context of the present work, *drug use incidence* will be used to refer to consumption of illicit substances ever in a person's life. In each of the scientific articles forming part of the thesis, the term "drug use" is clearly defined in accordance with the data source involved and the specific characteristics of each substance.

1.2 Brief history of drugs in Spain

Drugs illegal today such as cannabis, cocaine, heroin, have coexisted with humanity for centuries. However, attention focuses on these substances when they cause problems, especially at population level, and this leads to the epidemiological interest of consumption and a desire to contribute to action plans tackling the problem and its prevention. A clear example of this is how heroin distorted the lives of thousands of young people in Spain, perhaps of an entire generation, in the 80s and 90s.

Knowing the history of drug use in our setting will help us understand both the motivation behind this study of incidence and the actual results. Following Usó [5] and Gamella [6] among others, what follows is a brief tour of the history of drugs in Spain, from the early twentieth century to the present.

1.2.1 Before the Spanish civil war

At least until 1918 there was freedom to use any pharmacological substance in Spain. Any psychoactive substance could be used as we use pharmaceutical drugs today, to cure or relieve disease symptoms. However, demographic changes, particularly the massive influx of people to the large cities, meant that drug consumption for purposes other than conventional therapeutic uses began to spread. It was said that in the early 1900s there were around 6,500 cocaine users in Barcelona alone (bankers, soldiers, journalists, officials, people in showbusiness, ship's captains, ladies of the aristocracy, clergy, councilmen, etc). As a consequence of the scandal, government authorities were set up for the first time to control and restrict the use of drugs in Spain. This led to the appearance of a black market, and of new laws and penal code reforms. However, far from reducing the problem, drug use spread to include all social strata. In addition popular culture related to drug use, including magazines and other literature, became widespread.

At that time, the use of drugs was considered a vice or sin rather than an addiction. Drug users were practically all concentrated in major cities such as Madrid,

Barcelona and Valencia, and in the 30s the drugs most commonly used were cocaine and morphine.

1.2.2 During the Spanish civil war and Franco's regime

The civil war (1936-1939) changed this scenario substantially. The main change introduced by the war was the availability of cannabis. Indeed, the use of cannabis was already entrenched in the ranks of the rebel troops in North Africa, crossed the Strait of Gibraltar and spread across the country.

Until the 60s, the Franco regime effectively barred access to certain drugs and habits. This period is noted for the predominance of the following drugs:

- Amphetamines and barbiturates had a massive and widespread use, these types of psychotropic substances being known generically outside Spain as the "Spanish drug".
- Cannabis, mostly used among lower social strata and marginal settings, otherwise ignored.
- Morphine, for therapeutic use, but relatively easy to obtain.
- Cocaine, with fairly widespread use among the upper class and privileged Regime members.

In the mid-60s, "psychedelia" shook the international scene, Spain included, condemning the systematic poisoning of the population with "legal drugs" (alcohol, amphetamines, barbiturates ...), while advocating other substances with hallucinogenic effects such as marijuana and LSD. The phenomenon of youth tribalization meant that these drugs became a definitive part of youth subcultures (hippie movement, etc.). However, this period also saw an opportunistic resurgence of heroin, the consumption of which would be linked to elements from psychedelia and the counterculture, but did not become widespread until the late 70s.

1.2.3 The Spanish transition

By 1978, the most widely used illicit substance in Spain was hashish. That same year, the media drew attention to a new expansion of heroin use by injection, and there is still controversy over whether excessive media coverage at that time played some part in provoking curiosity about it. Nevertheless, the fact is that in 1978 there were only tens, or at most hundreds, of heroin injectors, whereas already by 1982 tens of thousands of young people had begun to inject opiates, available from a growing black market.

Throughout the 80s and 90s, consumption and trafficking of heroin generated significant social, legal and public health problems in Spanish society. The number of detoxification treatments, hospital emergencies and heroin-related deaths significantly increased. Because the most common route was injection, many communicable diseases became more prevalent. This period coincided with the emergence of human immunodeficiency virus (HIV), so that within a few years AIDS had acquired epidemic characteristics among heroin users and in the early 90's deaths due to AIDS outnumbered those from overdoses[7]. In addition, all this occurred in the context of a significant economic crisis.

The increase in crime eventually overlapped with and fuelled the expansion of intravenous use of heroin, and also of cocaine to a lesser extent. Solutions to treat the "problem" represented by this new social reality were needed. Accordingly, in June 1985, the "problem" found its way onto the political agenda, and the National Plan on Drugs was created.

1.2.4 The National Plan on Drugs

The *National Plan on Drugs* (NPD) was created as an interministerial organization seeking to respond to the social, health and crime problems related to illegal drug use, especially heroin at the time of its creation. One of the first actions of this organization was to establish a "new conceptual framework for treating heroin", which led to the creation of specific units for the treatment of dependence with the

intention of facilitating the integration of the user in their family, social and professional environment.

As the type of treatment promulgated was based on abstinence, a ministerial order placed restrictions on the use of methadone maintenance treatment (MMT) which had been initiated in 1983. The result was a decrease in the number of patients in MMT, which fell from 5,000 in 1985 to 1,000 in 1987. In other words, the first Drug Plan prioritized security policy and enforcement rather than public health policy. Unfortunately, between 1985 and 1990, the incidence of HIV among heroin injectors grew exponentially reaching prevalences of between 33% and 71% among heroin injectors [8, 9].

In 1990, after many public health professionals had demanded more pragmatic policies to deal with the HIV epidemic, the NPD changed the rules and restrictions affecting MMT [10]. Although it increased gradually, the use of MMT did not achieve a significant weight in treatment centers until 1995. Meanwhile, mortality rates among young people aged from 15 to 34 years increased from 65.7 per 100,000 in 1983 to 114.1 in 1990, the main causes of death being AIDS and heroin overdose [7, 11, 12].

After 1992, the heroin epidemic became endemic as shown by the decline in first treatment demands. Besides the decrease in numbers of heroin users, from 1991 to 1995 there was a tendency to switch from injection to other routes such as smoking or snorting. This also helped to reduce cases of HIV among drug users.

Heroin use in Spain overshadowed that of other illegal drugs. But since the 90's the pattern has changed: while heroin use has decreased, that of other substances such as cocaine, cannabis, ecstasy and amphetamines has increased progressively. This change was due to heroin becoming a stigmatized drug. People were aware of the horrible consequences of its consumption. Indeed, Musto has pointed out that drug epidemics eventually die when new cohorts observe the drug's ill-effects on their seniors [13]. On the other hand, the other drugs were associated more with recreation, partying, and discovering new experiences. Users also had the feeling

that these drugs were, if not innocuous, at least much less harmful than heroin. This trend has been maintained up to the present. Spain is among the European Union countries with the highest prevalences of cocaine and cannabis use (see section 1.4).

1.3 The Spanish Drug Observatory

In Spain, a lot of work has been done to counteract heroin use problems based on rehabilitation and prevention programs, either through projects promoted by the National Plan on Drugs or by non-governmental organizations, e.g. the "Proyecto Hombre". In addition, important follow-up studies have been conducted involving cohorts of heroin and cocaine consumers, such as the EMETYST project [40–42] and the ITINERE study ([14–39]) and others related to AIDS such as the project GEMES [43]. Nevertheless, data sources provided by the Spanish Drug Observatory are the most appropriate for studying the extent of drug use in the population.

The National Plan on Drugs created the Spanish Drug Observatory (SDO) in 1987, originally known as the State Information System on Drug Abuse, that mostly focused on the problematic use of heroin and cocaine. This observatory provides information and statistics on the evolution and characteristics of the use of psychoactive drugs (partially including alcohol and tobacco) and associated problems in Spain.

The main information systems focus on collecting data to elaborate three indirect indicators:

- admissions to detoxification treatment,
- hospital emergency admissions, and
- mortality from acute reaction related to drug abuse.

These indicators were established with the purpose of monitoring trends and patterns of problematic use of psychoactive drugs, especially those, such as opioids or cocaine, which produce problems more often and are difficult to explore with other methods. Other indirect indicators have been used like HIV/AIDS infection among drug users, drug seizures, etc, but we will not deal with them in this work.

Later, when heroin use began to decline and the use of other substances to increase, two series of biennial national surveys were launched:

- the National Survey on Drug Use in Secondary Schools began in 1994 (Encuesta Estatal sobre Uso de Drogas en Enseñanzas Secundarias - ESTUDES), and recruits students aged 14-18 enrolled in Secondary Schools, and
- the Household Survey on Alcohol and Drugs in Spain began in 1995 (Encuesta Domiciliaria sobre Alcohol y Drogas en España - EDADES), and recruits subjects from the non-institutionalized population aged 15-64.

These population surveys were reasonably well-suited to obtaining epidemiological indicators about general consumption, i.e. also including recreational use, not only for illegal substances like cannabis, cocaine, ecstasy, amphetamines, etc, but also legal substances like alcohol and tobacco. However, they were not so suitable for heroin because of the difficulty in contacting heroin users for interviewing, apart from the fact that in recent years their prevalence is very low.

In the following sections, the definitions and main findings of these indicators are presented. The results provided below focus on heroin, cocaine and cannabis, not only because these are the substances dealt with in this work, but also because they are the three most important illicit substances in terms of consumption in Spain. Note however that no results are available for incidence. From the following list of data sources, the present work focuses on only two that consistently collect information on first use, namely treatment admissions and EDADES.

1.3.1 Treatment admissions

This indicator is derived based on a register that contains information relating to outpatient treatment admissions for psychoactive substances abuse or dependence. Of interest for our purposes, treatment admission records contain information about the patient's first use of the main drug to be treated. Admissions for heroin and cocaine started in 1987 and cannabis and other illicit substances started in 1996. In addition, as from 1991 onwards, the data record specifies whether the admission is the first time in the user's life for the particular drug involved or a relapse. Note that this information is essential to study the incidence of drug use.

Among other valuable information which can be extracted from this indicator, it is interesting to observe the distribution of treatment admissions over the years. By distinguishing people admitted to treatment for the first time in their life from those who have been treated previously, one is able to see the direction of the trend in the numbers of new consumers (i.e. a proxy of incidence). Trends in treatment admissions, first and relapses, are shown in figure 1.2, where it may be observed that first admissions for heroin began to decline after 1992, while both cocaine and cannabis have been increasing since the early 90's [44].

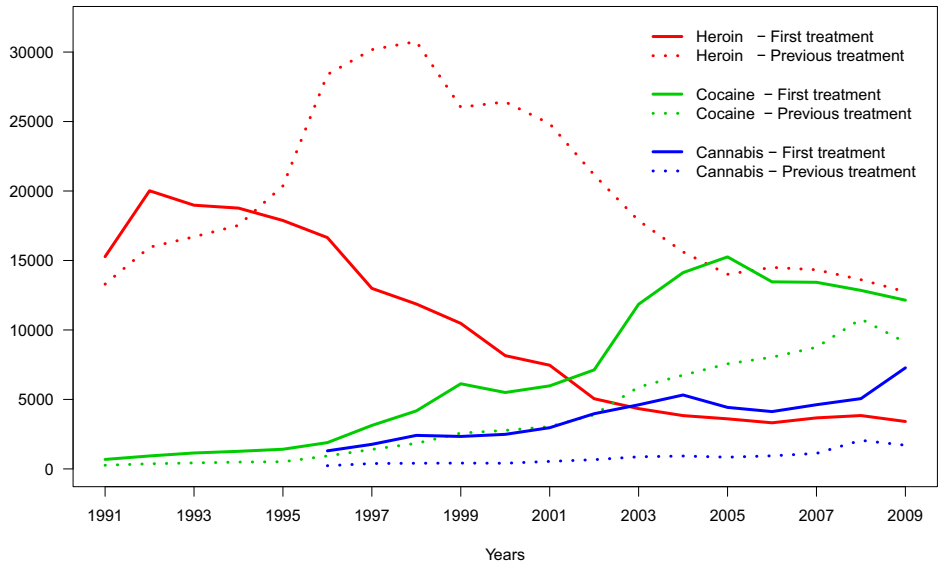

Figure 1.2: Evolution of treatment admissions of drug users in Spain (absolute number)

Another very interesting aspect may be seen in figure 1.3 which represents the evolution in Spain of the proportion of first treatment admissions of heroin users that were injecting when they sought treatment. Although, overall, incidence of heroin use decreased in Spain, trends in the use of the intravenous route differ between regions.

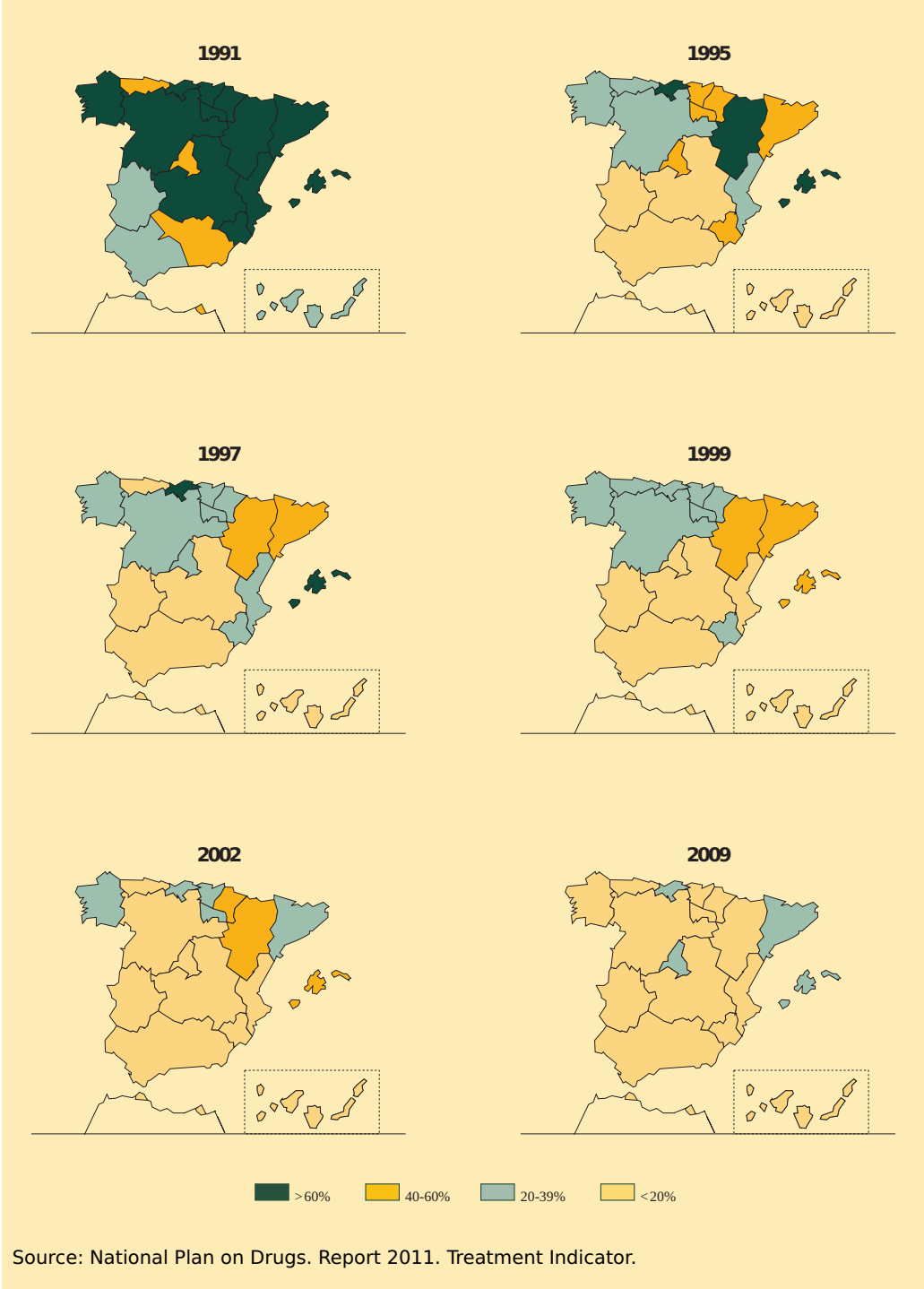

Figure 1.3: Evolution of the proportion of first treatment admissions among intravenous heroin users in Spain.

1.3.2 Hospital emergency admissions

This indicator is intended to monitor the characteristics of hospital emergencies related to non-medical use of psychoactive drugs in Spain, excluding alcohol and tobacco. This includes all hospital emergency episodes occurring in a specified time period, usually one week a month, in people aged 15-64.

Figure 1.4 shows that emergencies related to heroin have been losing protagonism [44]. Meanwhile, emergencies related to cocaine and cannabis have increased, to the point that cocaine has been mentioned more frequently than heroin since 1999, and cannabis more frequently than heroin since 2004.

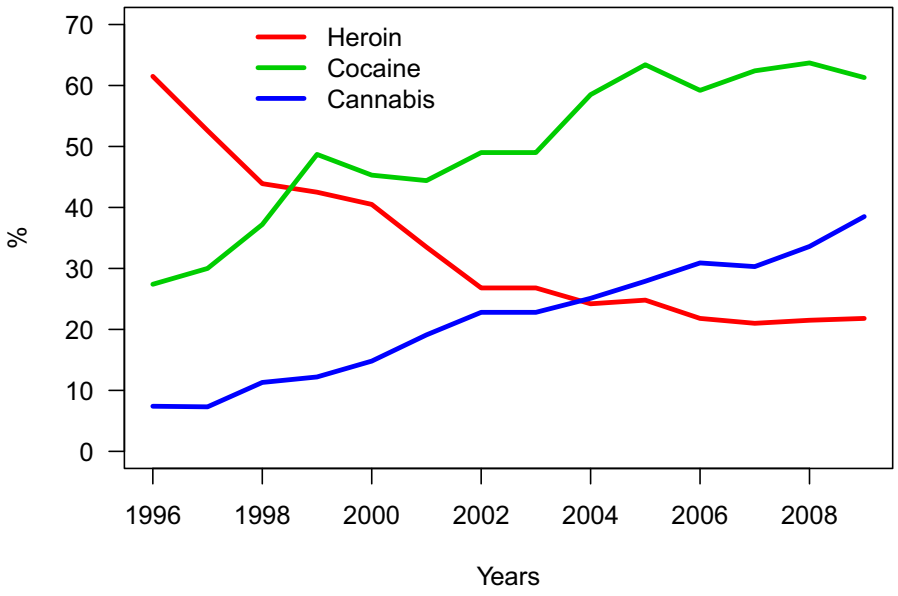

Figure 1.4: Evolution of hospital emergencies (%) related to drug use in Spain.

1.3.3 Mortality from acute reaction related to drug abuse

This indicator includes information on those deaths requiring an autopsy, for which the underlying cause of death is an acute adverse reaction (overdose) after non-medical or intentional use of psychoactive substances (excluding alcohol and tobacco).

Figure 1.5 shows an estimation of the evolution of deaths by acute reaction related to the use of psychoactive substances [44]. In general, the rapid increase observed during the 80s, associated with intravenous heroin use, is followed by a downward trend in mortality that continued at least until 2009. The majority of these deaths involve consumption of opiates.

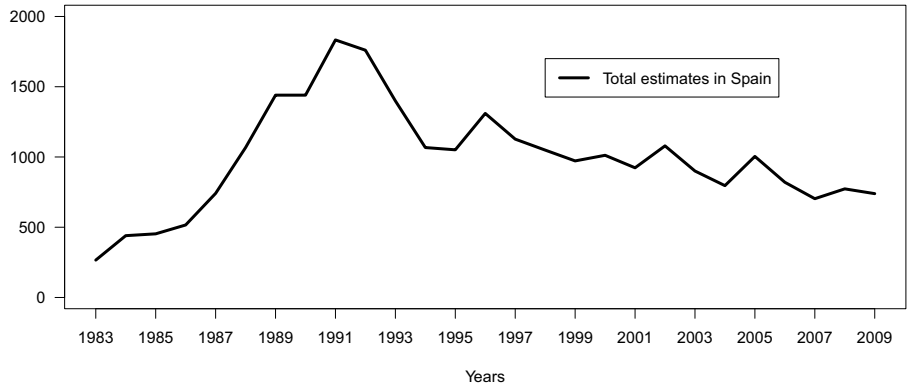

Figure 1.5: Evolution of deaths by acute reaction related to drug abuse.

1.3.4 EDADES

The EDADES series of surveys, taken all together, provide time series which allow us to analyze trends in the prevalences of alcohol, tobacco, hypnosedatives and illegal psychoactive drugs. In addition, the survey provides information about dominant consumption patterns, consumer profiles, social perceptions of the problem and measures considered by lay people to be the most effective to combat drug abuse. Moreover, the questionnaire and methodology are quite similar to those used in other European Union countries and the United States, thus allowing international comparisons.

Prevalences are reported referring to lifetime use, last 12 months, last 30 days, broken down by sex and autonomous community (Spanish regions). Other useful information shown in the reports is the average age at first use. Figure 1.6 shows lifetime prevalences of heroin, cocaine and cannabis and figure 1.7 the corresponding average ages at first use [44]. Prevalence estimates apparently show an increasing trend for cannabis and cocaine and stable ages at first use. No information is provided for variability.

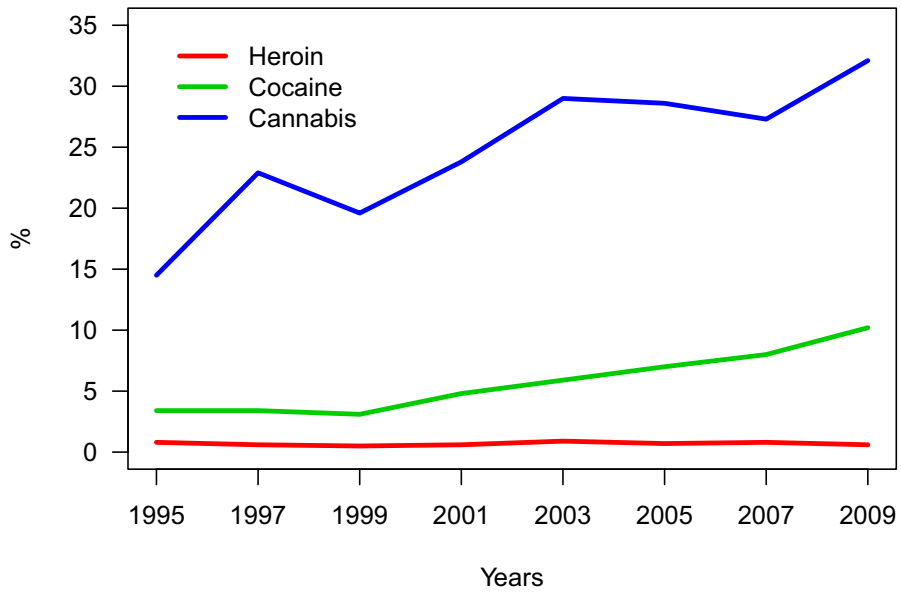

Figure 1.6: Evolution of lifetime prevalence (%) of drug use in the Spanish population aged 15-64 years.

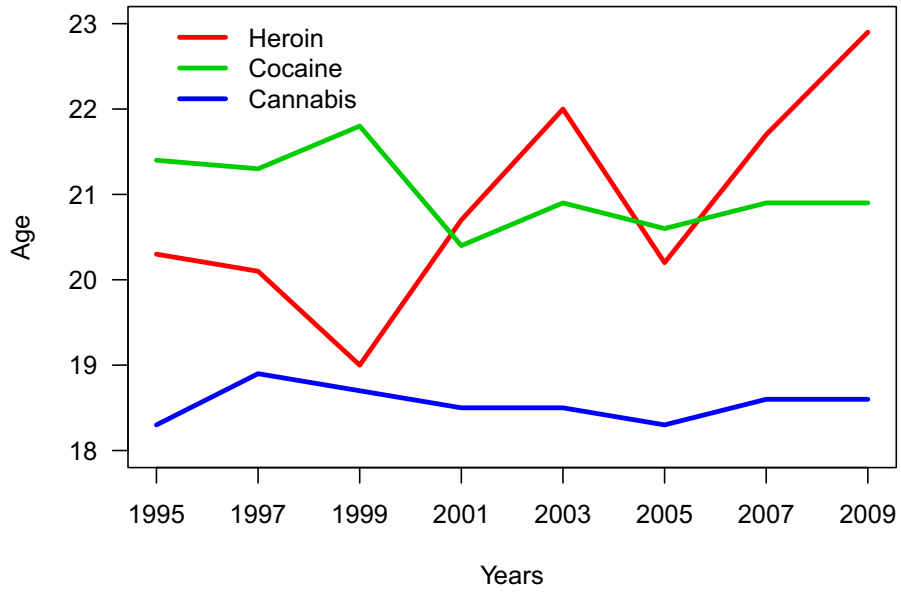

Figure 1.7: Evolution of the average age at first drug use in the Spanish population aged 15-64 years.

1.3.5 ESTUDES

The ESTUDES series of surveys have had the same general aims as the EDADES surveys, although focused on students aged 14-18 enrolled in Secondary Schools of Spain.

Regarding the evolution of prevalences of illegal psychoactive drugs, in 2010 the percentage ranking order is similar to that reported by EDADES, maintaining almost the same percentage of lifetime prevalence of cannabis use (33%), while that for cocaine is much lower (3.9%). Figures 1.8 and 1.9 show the evolution of lifetime prevalences and the average age at first drug use [44]. Prevalence estimates of cannabis and cocaine show decreasing trends from 2004 onwards, in contrast to the increasing trend observed in EDADES. Possibly, high prevalences in young age cohorts before 2004 have moved to older age cohorts, now only visible in EDADES. No information is provided for variability.

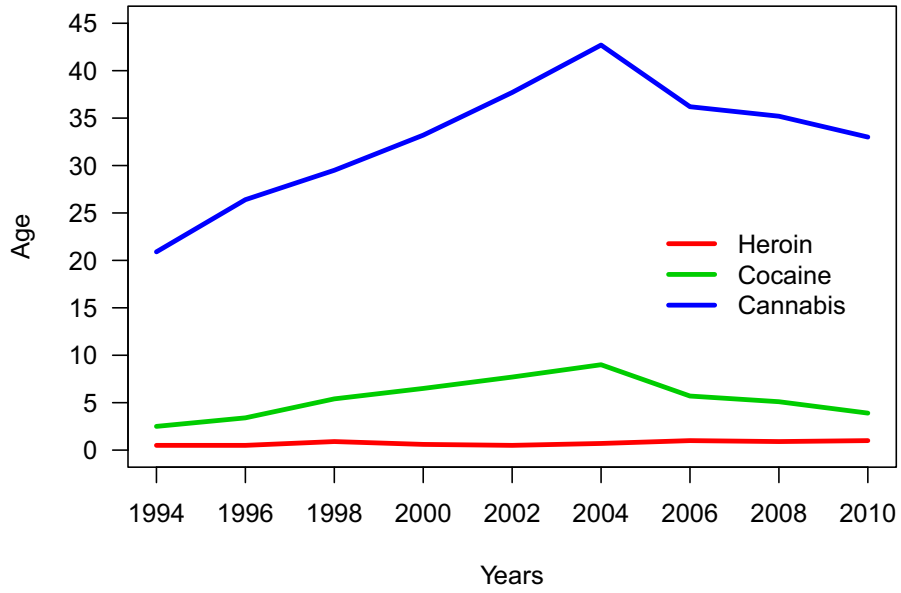

Figure 1.8: Evolution of lifetime prevalence (%) of drug use among Spanish secondary school students aged 14-18.

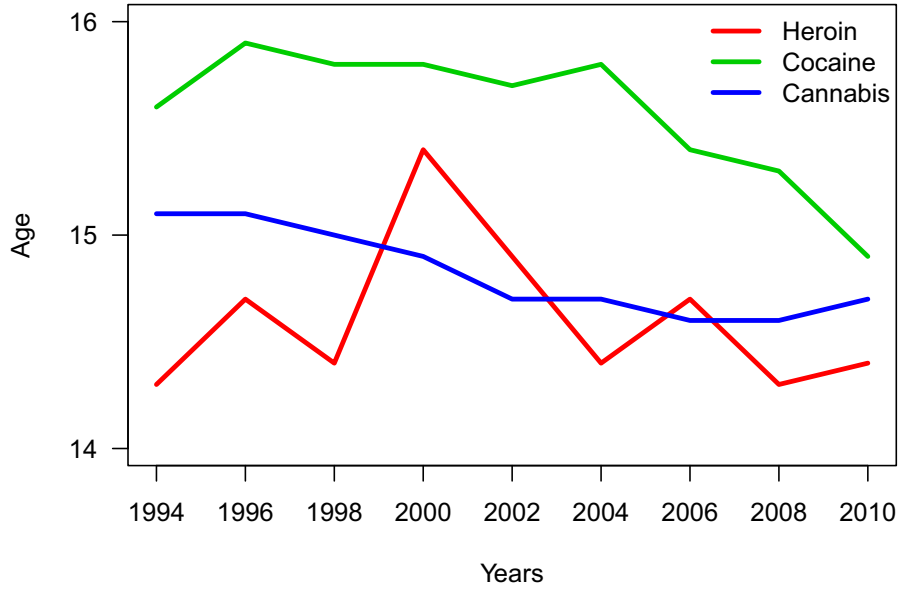

Figure 1.9: Evolution of the average age at first drug use among Spanish secondary school students aged 14-18.

1.4 Comparison with other countries

Since last century, advances in chemistry and pharmacology have allowed new drugs to be created from old raw materials like opium, coca or amphetamines, and thanks to globalization this knowledge has spread. For this reason, the problem of drug use has become worldwide, affecting both developed and developing countries.

Regarding drug use epidemiology, the first references come from the United States, where heroin use became a national problem in the late 60's and 70's. The expansion of heroin use in Europe, including Spain, really began 10 years later, and persisted during the 80's and early 90's. Since then, heroin use has been decreasing in Western Europe. Recent reports of prevalences for opioid/heroin use in various European countries indicate that Spain now has medium prevalence levels (figure 1.10) [45].

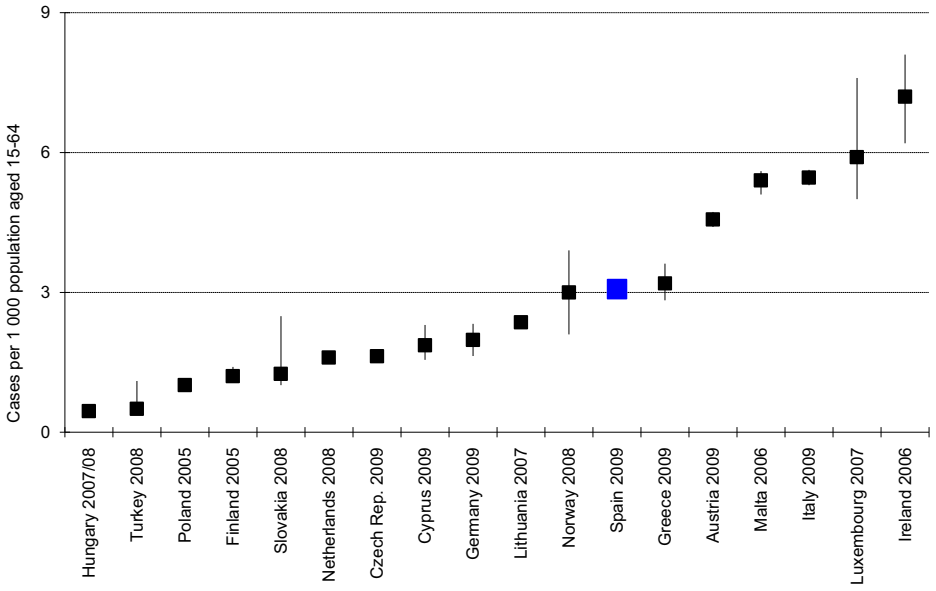

Figure 1.10: Estimates of the prevalence of problem opiod use (rate per 1000 population aged 15 to 64), 2004 to 2009 - last study available

As for heroin, the first references to the problem of cocaine use are from the United States, mostly in the 80's. Again, around 10 years later, the problem began to rise in Western Europe; meanwhile there are recent reports that in North America use is declining. Spain has one of the highest prevalences of cocaine use in Europe (figure 1.11) [45].

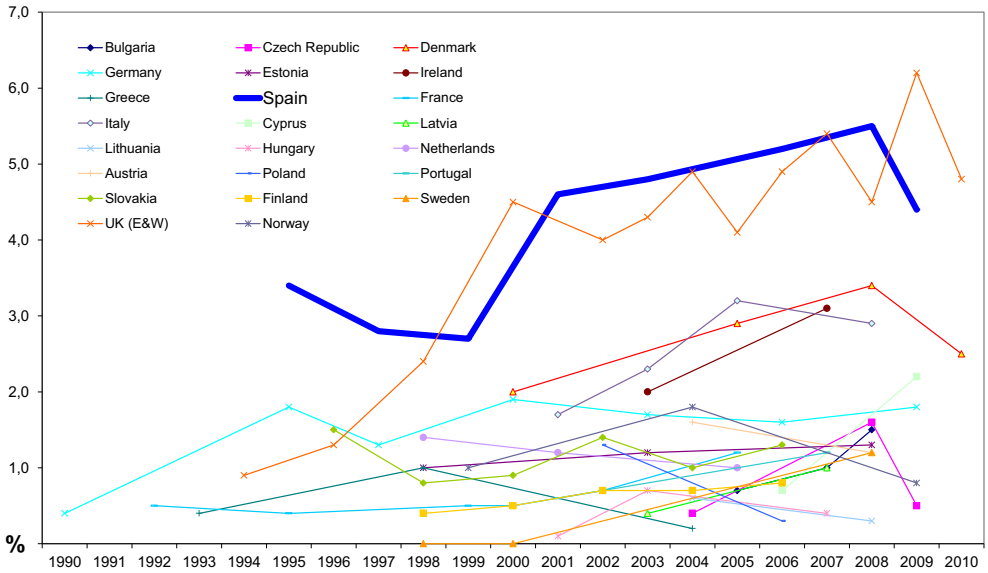

Figure 1.11: Trends in last 12 months prevalence of cocaine use among young adults (aged 15 - 34)

In contrast to heroin or cocaine, cannabis plants grow easily in many different climates and require no processing for use. For this reason and because of the lower levels of physical harm and dependence associated with its consumption, cannabis remains the most widespread illicit drug in use worldwide. Cannabis use is increasing overall, but in some regions, notably North America, Russia, China, and parts of Asia, its use has stabilized or decreased in recent years. In Europe, since the 90's, its prevalence is generally tending to increase, with Spain currently having one of the highest prevalences (figure 1.12) [45].

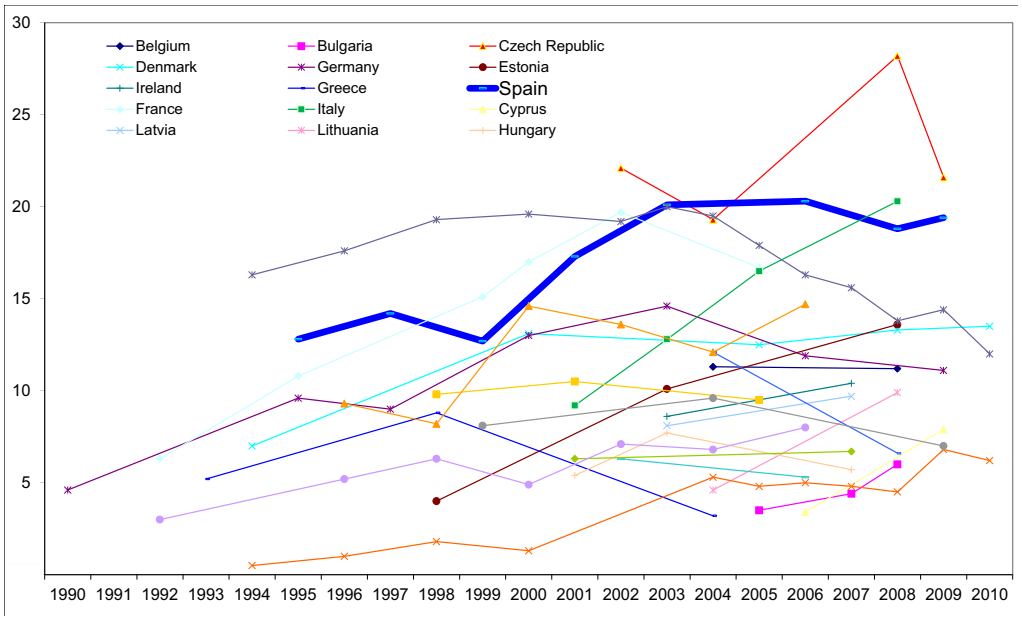

Figure 1.12: Trends in last 12 months prevalence of cannabis use among young adults (aged 15 - 34)

1.5 Justification

As seen in section 1.1, incidence is a far more important epidemiological measure than prevalence, because it helps us to see the dynamics of the epidemic, enabling more timely implementation of prevention policies. The great epidemic of heroin use in Spain caught the country off guard: prevention policies were nonexistent and it took too long to respond. Regarding cocaine use, prevention policies, based on indirect indicators, were probably alerted to an increase of cocaine use towards the end of the 90's. However, prevalences were increasing dramatically, and eventually reached figures that were the highest in Europe. It is therefore possible that prevention policies also arrived rather late, as the rise in incidence had already occurred several years before.

Since around 2000, the EMCDDA has been supporting drug experts from all European countries in the development and use of statistical techniques to estimate the incidence of drug use. In 2008, a guide for estimating incidence was published with the aim of reducing the methodological difficulty for drug expert epidemiologists and encouraging them to apply it to their country. However, the application of these methods is still far from trivial, highlighting the need for this type of work to be assigned to appropriately trained biostatisticians.

Given these considerations the present work, providing incidence trends for different substances, is noteworthy because:

- incidence of drug use is a very important epidemiological indicator for prevention,
- the development of statistical methods to estimate the incidence of drug use is currently being actively promoted in Europe, and
- incidence of drug use can provide a new indicator of particular interest for public health policy-makers in Spain.

Learn from the mistakes of others.
You can never live long enough to
make them all yourself.

Groucho Marx

CHAPTER

2

State of the art

In epidemiology, incidence is idealistically calculated by tracking a representative sample cohort of susceptible individuals, following them over time and noting how many develop a disease or, in our case, use an illicit psychoactive drug for the first time. However, apart from the usual difficulties involved in following up a healthy cohort, people usually hide their use of such drugs, as we have seen in section 1.1. Therefore, prospective studies investigating drug use incidence are very difficult to carry out. In the United States, some prospective or longitudinal design studies have been conducted where information about first drug use was collected. Most of the cohorts involved adolescents and efforts were made to check patterns and associations with other behaviours, relationship with licit substances, risk of mental disorders, etc [46–50]. Ritter and Anthony (1991) undertook a study based on data from two waves of surveys in the general population, although they only studied factors associated with the risk of becoming a cocaine user [51]. Similarly, Perez et al (2010) studied cannabis consumption initiation among adolescents in Barcelona [52].

Another way to obtain data on first drug use is by asking users themselves when they make contact with some administrative center, for example when requesting detoxification treatment, or even when they are questioned in any survey, provided

total confidentiality is guaranteed. So, data on first drug use are collected retrospectively, and then, incidence figures can be tabulated retrospectively. However, incidence figures obtained this way are incomplete and lead to wrong conclusions. For this reason, we must resort to using more sophisticated statistical methods.

This chapter will review the methodological approaches that preceded those presented in this work. These previous approaches are: the lag-correction method (section 2.1), the back-calculation method (section 2.2), and the composite retrospective estimation of incidence from periodic surveys (section 2.3).

The lag-correction and back-calculation methods are related. Both begin by obtaining a distribution of the lag time, i.e. the time elapsed between an individual's first drug use and their first contact with some administrative register, usually a treatment centre. The lag time distribution is very useful because by asssuming this distribution represents a common pattern, missing information about first drug use can be recovered. On the other hand, the third approach uses the reports of first drug use obtained from interviewees in population surveys. The fact of combining data from several cross-sectional surveys performed at different times in the same population should yield incidence figures with better properties.

There is an important editorial by Hickman entitled: "The diffusion of heroin epidemics: Time to re-visit a classic" [53], highlighting the importance of taking account of earlier epidemiological studies about drug use. Efforts to develop approaches tend to occur when problems related to the use of some substance become widespread in society. For this reason, literature reviewed in the present work was focused on the first studies conducted in the United States during the 70's (heroin epidemic), and those 10 to 20 years later in Europe and Australia.

2.1 The Lag-Correction method

Treatment registers usually provide regularly collected data. So, data sources of this kind tend to be the most widely available and complete. Moreover, they usually record individual information about the patients. If information is available about when these patients started their drug use, incidence figures can be obtained by tabulating it retrospectively in discrete time intervals. However, incidence obtained in this way is *right truncated* as we cannot take into account people entering their first treatment at a time later than the last year observed. Incidence figures obtained by tabulation are therefore underestimates, the degree of underestimation becoming gradually more serious with time. The lag-correction method attempts to solve this underestimation.

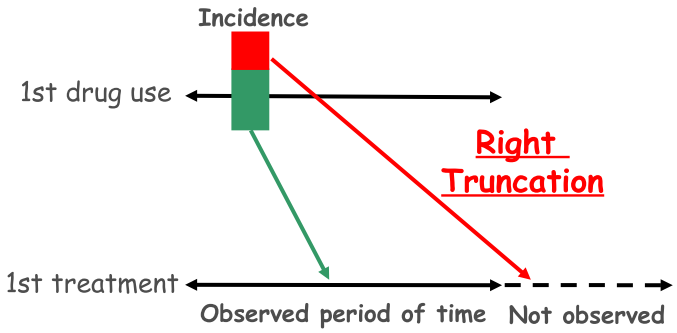

Figure 2.1: An example of right-truncated incidence.

Apart from this progressive underestimation, note that such incidence figures are based on problematic drug users, since only individuals entering treatment are taken into account. The lag-correction method does not attempt to solve this limitation.

2.1.1 Literature

The lag-correction method was first discussed by Hunt et al in 1974 to estimate incidence of heroin use in the United States [54]. Shortly thereafter, in 1976 Hunt and Chambers published the book "The Heroin Epidemics" [3]. In this book they formalised the estimation of incidence of heroin use accounting for the spread of

new users in two ways: microdiffusion, referring to the diffusion (or transmission) between individuals, and macrodiffusion, i.e. between cities and regions. Moreover, they introduced the terms "lag time", the time between first use and first treatment, and the "lag-correction method". They assumed the lag time to be stable and, because of sample variations, the absolute size of the current year's incidence was of little concern, more importance being attached to the incidence trend. However, they were criticised, mainly because the method involves many untestable assumptions, and they were convinced that population surveys would provide better information [55].

Later, Hickman et al reintroduced the method to estimate the incidence of heroin use in treatment data from southeastern England [56]. Although applying basically the same methodology, they were able to benefit from technical improvements resulting from its use in AIDS research. Many articles have been published in the AIDS field about this correction, where it is known as the "reporting delay adjustment method". The number of AIDS cases reported to surveillance centers had been found to seriously underestimate the number of recent AIDS diagnoses, because of substantial delay in reporting [57–65]. Hickman et al saw there was a clear similarity and adapted the method to the drug use context.

Nordt and Stoler applied it to estimate incidence of heroin use in Switzerland [66, 67]. We also applied this method previously (i.e. not as part of the present thesis work) to estimate incidence of heroin and cocaine use in Barcelona [68]. And Scalia-Tomba et al included the method in the EMCDDA's guidelines [69].

2.1.2 Formulation

The idea behind lag-correction is that the time between the onset of drug use and first treatment ever follows some kind of pattern, usually represented by a non-parametric distribution. This distribution acts as an inflation factor, raising incidence figures and thus compensating the underestimation.

We consider discrete time. Let i be an indicator of calendar time from 1 to I, coinciding with a period when treatment data are observed. From people entering treatment for the first time in their lives, we tabulate their first drug use within the period from 1 to I. The number of new drug users for each i is the observed incidence (see figure 2.2).

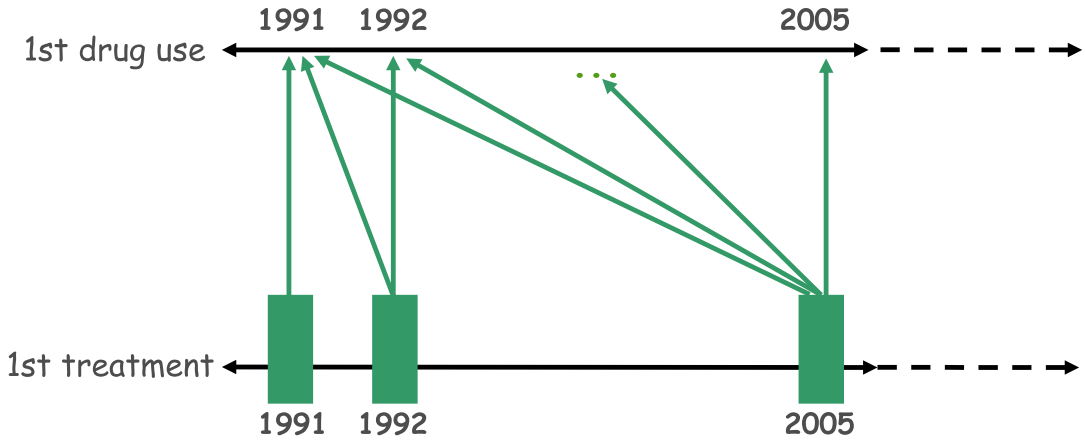

Figure 2.2: Observed incidence from first treatment episodes in the period of time from 1991 to 2005.

Let h_i be the observed incidence in $i = 1, \ldots, I$. Note however that people who started drug use at a time $i = 1, \ldots, I$ but who were not admitted for their first treatment until some time later than I, are not observed (right truncation).

Therefore, incidence can be estimated as follows:

$$\hat{h}_i = \frac{h_i}{F(I-i)}\,, \tag{2.1}$$

where

$$F(t) = P[d \leq t] \tag{2.2}$$

is the lag time distribution.

Formula (2.1) says that for a fixed number of individuals starting drug use in year i ($\hat{h}_i$), a subset/proportion of them (h_i) started first treatment within a lag time of $I - i$ (see figure 2.3).

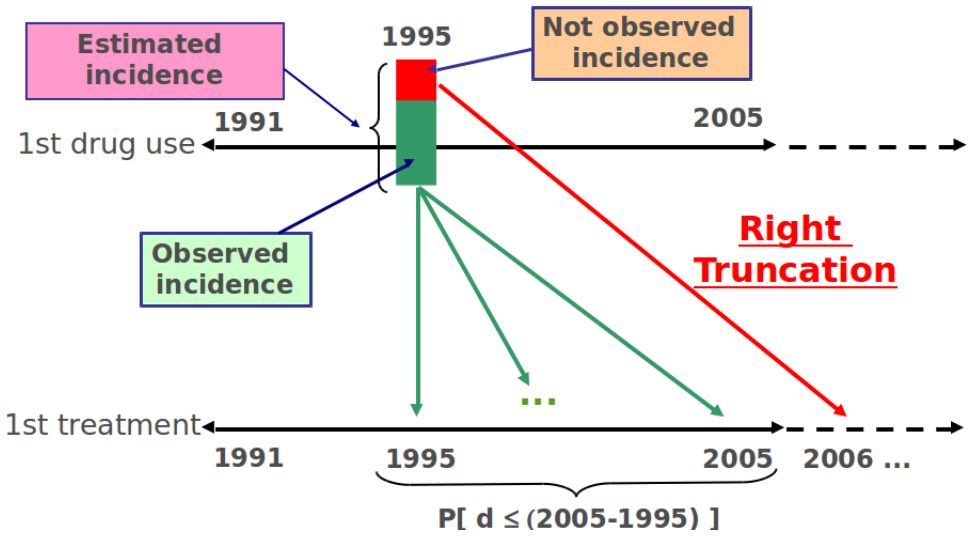

Figure 2.3: A graphical example of the lag-correction method.

The non-parametric conditional lag time distribution

According to Brookmeyer and Liao [62], there are two computationally attractive methods for obtaining this distribution: one is based on Poisson regression which is used in the first article of the present work and explained in section 4.1; the other is an adaptation of survival analysis and life table techniques for use with right-truncated data and is explained below.

Brookmeyer and Liao's formulation [62] (and Hickman et al's adaptation [56]) originates in the work of Kalbfleisch and Lawless [63] and of Lagakos et al [60], representing two slightly different approaches but which yielded identical estimates. Kalbfleisch and Lawless constructed a likelihood function based on the fact that observed initiating events correspond to a non-homogeneous Poisson process with intensity $h(i)F(m-i)$, where $F(t)$ is the unconditional lag time distribution as in 2.2. This distribution cannot be estimated with data of this type. Since only conditional probabilities can be estimated, we define:

$$G(t) = \frac{F(t)}{F(m)}, \quad t = 1, \ldots, m, \tag{2.3}$$

where m is the maximum observed lag time and $G(t)$ is the conditional lag time distribution (conditional on lag being $t \leq m$). Let d denote lag time:

$$G(t) = P\left[d \leq t | d \leq m\right], \quad t = 1, \ldots, m. \tag{2.4}$$

If f and g are the probability mass functions of F and G, respectively, then from equation 2.3, we have the following:

$$g(t) = \frac{f(t)}{F(m)}, \quad t = 1, \ldots, m. \tag{2.5}$$

The key point here is that they defined a function $g^*(t)$ which only depends on t:

$$g^*(t) = \frac{f(t)}{F(t)} = P\left[d = t | d \leq t\right], \quad t = 1, \ldots, m. \tag{2.6}$$

This function is so defined with the specific purpose that the conditional lag time distribution can be obtained from the following recurrent identity:

$$G(t) = (1 - g^*(t))G(t+1), \quad t = m-1, \ldots, 1. \tag{2.7}$$

where $G(m) = 1$.

In the work of Lagakos et al [60], equation 2.6 was interpreted as a discrete hazard function and equation 2.7 taking the form of a product-limit :

$$G(t) = \prod_{d=t+1}^{m} (1 - g^*(d)), \quad t = m-1, \ldots, 1. \tag{2.8}$$

The only people who can contribute information about $g^*(t)$ are those whose truncation times are $\geq t$ and whose lag times are $\leq t$. We call the set of all such individuals the "risk set" at time t. The number of individuals in the risk set is denoted by n_t, while the number in the risk set who have a lag time equal to t is Y_t. Therefore, the non-parametric estimator of G is:

$$\hat{G}(t) = \prod_{d=t+1}^{m} \left(1 - \frac{Y_d}{n_d}\right). \tag{2.9}$$

For this reason, Brookmeyer and Liao [62] commented that this approach is analogous to the product-limit of Kaplan-Meier [70].

Therefore, equation 2.1 is modified as follows:

$$\hat{h}_i = \frac{h_i}{\hat{G}(I-i)}, \quad i = 1, \ldots, I. \tag{2.10}$$

2.1.3 Some remarks

There are two important limitations to be aware of:

- corrected incidence is "relative" to the maximum lag time observed, and
- treatment availability (supply) should be stable throughout the study period, as the conditional lag time distribution is being used under the assumption that it does not vary with time.

Therefore, incidence may be underestimated due to the presence of drug users with longer lag times than those observed, and the incidence trend could be biased if treatment supply really did vary in practice.

In any case, as EMCDDA's guidelines advise, this approach is suitable for implemention in localised areas where data are more accessible and possible changes in treatment supply can be easily tackled [69].

2.2 The Back-Calculation method

Like lag-correction, this method is usually focused on treatment data. The distinctive feature is that there is no need to have individual information. Only knowing the yearly number of first treatment cases and resorting to an external lag time distribution, an estimation of incidence is possible. The lag time distribution is usually parametric because its use only requires a few parameters such as mean and variance and adoption of a suitable distribution pattern (e.g. a Weibull distribution).

As the lag time distribution can be constructed externally as a parametric distribution, there is no maximum lag time restraint. Therefore, although the observation time period of any particular treatment register is limited, it can be used to obtain incidence estimates applying to a period of time longer than actually covered by the register.

2.2.1 Literature

This method was first proposed by Brookmeyer and Gail in 1986 to estimate the HIV infection curve on the basis of AIDS incidence data [71]. Later, more sophisticated back-calculation methods were implemented, also in the AIDS field[59, 65, 72, 73].

The EMCDDA adapted the method to the drug use context around the year 2000 in the framework of an European multi-site collaborative project. As for the lag-correction method, the lag time between first drug use and first treatment was considered analogous to the incubation time of HIV. They applied the method to estimate incidence of heroin use in Amsterdam and Italy with the aim of higlighting the main peculiarities of the proposed approach and to make comparisons. In 2003, EMCDDA's experts also tried to estimate incidence of opiate use in Spain based on treatment data. They constructed three different lag time distributions, corresponding to treatment data from the years 1992, 1996 and 2001, with mean lag times of 5 years, 7 years and 9 years, respectively. Figure 2.4 shows the three

different incidence curves. Spanish drug experts were not convinced by these results and considered that more analyses were needed. Finally in 2008, the method was incorporated in the EMCDDA's guidelines[69].

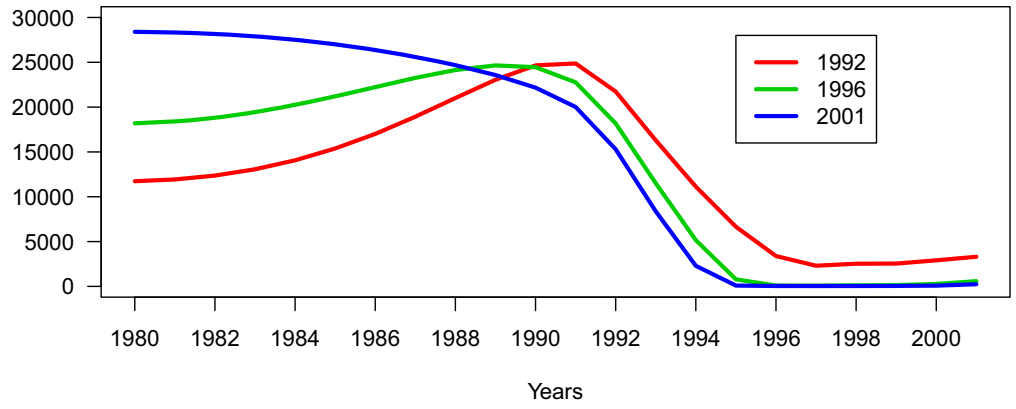

Figure 2.4: Back-calculation estimate of the incidence of heroin use in Spain

Interestingly, in 2004 De Angelis et al used this method to estimate incidence of opiate use/injecting drug use in England, considering the lag time to be that between first drug use and overdose death, instead of first treatment[74].

2.2.2 Formulation

Back-Calculation is a general type of deconvolution method by which it is possible, from data on drug users already observed (i.e. admitted to treatment), to determine the incidence of onset of problematic drug use among those who have yet to be observed. Aggregated data on users attending treatment for the first time and a lag time distribution, that can be provided by external information, are all that is needed to back-calculate the incidence of first use.

Let us consider year probability mass functions at onset and at treatment. We will denote the former by $h(i)$ (unknown), where i is the year of onset, and the latter

by $g(j)$ (assumed known), where j is the year of first treatment. Let t denote the lag time, given by $t = j - i$. Such functions are linked by the following equation:

$$g(j) = \int_{s=0}^{j} h(s)f(j-s)ds,$$

where f is the density function of the lag time distribution. This distribution is constructed externally and usually as a parametric distribution.

Regarding estimation of the function $h(\cdot)$ (incidence), the EMCDDA's incidence guidelines remark that three different methods have been employed with drug use data: empirical Bayes[4, 75], Bayes MCMC[76], and smoothed Expectation-Maximization[74].

2.2.3 Some remarks

According to the EMCDDA's incidence guidelines, back-calculation may be applicable if the only data available are the aggregated totals from first treatment ever [69]. For this reason, an external estimate of lag time distribution is needed. However, they also say that regardless of data source, the time, place and circumstances under which the data were collected were probably different from those related to the data set under consideration. It is essential for the correctness of the incidence estimates that the lag time distribution used be the most appropriate possible, and using a "wrong" lag time distribution will result in "wrong" incidence estimates. In other words, incidence results are very dependent on the the assumed external lag time distribution.

2.3 The Composite Retrospective Estimator

In cross-sectional studies, incidence can be obtained from retrospective self-reports of age at first use of the substance, tabulated by calendar year.

2.3.1 Literature

Relatively few cross-sectional studies have analysed incidence. Some studies have estimated age-specific incidence rates [77–79], some have estimated age-specific cumulative incidences by birth cohorts [80–83], some have determined hazard rates of age of drug use initiation [84, 85], and others have estimated yearly incidence [81, 86–89]. Regarding the latter, [81, 87] estimated yearly incidence from a single survey. However, already in 1992 Gfroerer et al combined the samples of several population surveys to estimate incidence of illicit drug use in the United States [86]. They have called their method "composite retrospective estimation", sometimes abbreviated to "the retrospective method". According to these authors, incidence estimates obtained retrospectively via periodically repeated samples drawn from the same target population should permit more robust estimates of overall incidence trends, while possibly reducing biases. In fact, their incidence estimate is "merely" a weighted mean of the incidence figures from the different surveys. As far as we know, this composite estimator has only been used in two studies [88, 89] .

These cross-sectional studies have mostly dealt with licit substances like alcohol and tobacco and illicit substances like cannabis and cocaine. These illicit substances can be included because consumers have low fear of disclosure and their prevalences are reasonably large. However, heroin use is not so well-accepted and the different lifestyle of heroin users makes them difficult to reach. Gfroerer et al already pointed out that incidence estimates of heroin use were too unstable to permit obtaining a valid trend.

The following subsection reproduces the formulation employed by Gfroerer et al, and on which the third article of this thesis was based.

2.3.2 Formulation

For each interviewee, the calendar year of their first use ever is tabulated retrospectively. In this way, from all interviewees of the sample we obtain yearly incidence figures according to their weights in the population. Combining these incidence estimates for all surveys, Gfroerer et al developed the composite estimates of incidence as follows:

$$X_i = \sum_{j>i+1} W_{ij} \cdot X_{ij} \tag{2.11}$$

where i is the calendar year, j is the survey year, X_{ij} is an incidence estimate for year i and survey j, and W_{ij} is the weight for year i and survey j, which is calculated as follows:

$$W_{ij} = \frac{(Var(X_{ij}))^{-1}}{\sum_{j>i+1}(Var(X_{ij}))^{-1}} \tag{2.12}$$

They estimated the variances of each X_{ij} using a statistical software package for analyzing complex sample survey data.

2.3.3 Some remarks

Gfroerer et al suggested that subsequent analyses should include estimates of incidence rates for age cohorts, and also, that these analyses should evaluate the impact of biases on the estimates [86]. Johnson et al [90] and Gfroerer et al [91] assessed these biases and concluded that respondents in general had a fear of disclosing their drug use, except for tobacco, and that recall errors were less serious for recent than for earlier years.

The United States National Household Survey on Drug Abuse did not present findings for incidence of consumption as they considered that the magnitude of the estimates lacked validity. On the other hand, Gfroerer et al considered that, apart from their lower cost, these retrospective estimates have certain analytical advantages. When data are obtained for different periods from the same respondents, trend analyses are more powerful [91].

Standing on the shoulders of giants.

Bernard of Chartres

CHAPTER

3

Hypotheses and aims

3.1 Hypotheses

The main hypotheses of the present work are:

- As heroin abuse usually leads to dependence and rapid health impairment, treatment registers are a suitable data source for estimating incidence. The good coverage of treatment data in Spain and the fact that lag times between the start of heroin use and the first treatment ever are not too long also contribute to their suitability.

- Treatment data are not suitable for estimating incidence of cocaine and cannabis users. A considerable proportion of them never attend any treatment center, and in any case lag times until starting treatment are very long.

- In Spain, general population surveys can obtain a large number of cocaine and cannabis users because consumption is prevalent in Spain, and most consumers lead a normal life, so they are eligible for recruitment into the samples and do not have too great a fear of disclosing their behaviour.

3.2 Aims

The general aims of the present work are:

- Estimate incidence trends for heroin, cocaine and cannabis use in Spain since the 70's.
- Develop methods more appropiate for the context and type of data available in Spain.
- Assess adequacy of the different methods for comparing the estimated incidence trends.

In article 1:

- Using only treatment data, we wanted to estimate problematic incidence trends of heroin use conditional on users surviving at least to the start of their first treatment.
- Apart from correcting incidence for right-truncation, i.e. heroin users who had still not started any treatment by the last year observed, we also wanted to correct for left-truncation, i.e. heroin users who had already been treated before the first year observed. This made it possible to obtain incidence estimates beginning in the 70's.
- As the lag-correction method is conditional to a maximum lag time of the length of observed period of time, our aim was to extend this maximum lag time as much as possible.

In article 2:

- To take the definition of problematic use incidence further by incorporating a proportion of individuals who use heroin but never show up in treatment, either because they die or permanently cease their heroin use.
- To avoid using a fixed lag-time distribution, because we know treatment demand was not stable over the period studied.

In article 3:

- Estimate incidence trends of cannabis and cocaine use ever from general population surveys.
- Standardize yearly incidence estimates to account for changes over time in the age structure of the Spanish population.

Part II

Contributions

The data is all over the place, the insight is yours, and now an abacus is at your disposal, too.

Judea Pearl

CHAPTER

4

Summary of articles

The methodological approaches seen in chapter 2 can be used to estimate the incidence of drug use in Spain. However, given the nature of the Spanish data, these previous methods involve limitations that we wanted to overcome, using those presented in this work, even though they, in turn, have certain other limitations.

Section 1.3 presents data sources available in Spain containing epidemiological indicators. From them, only treatment data and the EDADES surveys contain individual information about first drug use. Therefore, these data sources are potentially suitable for making inferences about incidence of drug use in Spain.

The following sections present a summary of each article. More details can be found in the articles themselves (see chapter 8). Moreover, the first 4.1 and second section 4.2 include some extensions that were not included in the corresponding articles.

4.1 Article 1: Loglinear model of quasi-independence

The first article *Problematic heroin use incidence trends in Spain* (annex section 8.1) deals with data from treatment registers in Spain, collected between 1991 and 2005. Briefly, these data were cross-tabulated, thus creating a table of frequencies where rows represent years of first heroin use, between 1971 and 2005, and columns correspond to lag time in years between first heroin use and first treatment ever, ranging from 0 to 34 years. This table was incomplete as two subsets of cells were missing (see figure 1 from article 1 section 8.1). One of these subsets was caused by people starting heroin use before 1991 and entering first treatment also before 1991, which we called "left truncation". The other subset was the one named "right truncation" in section 2.1.2 ("lag-correction method"). Figure 4.1 provides a simple overview of these truncations.

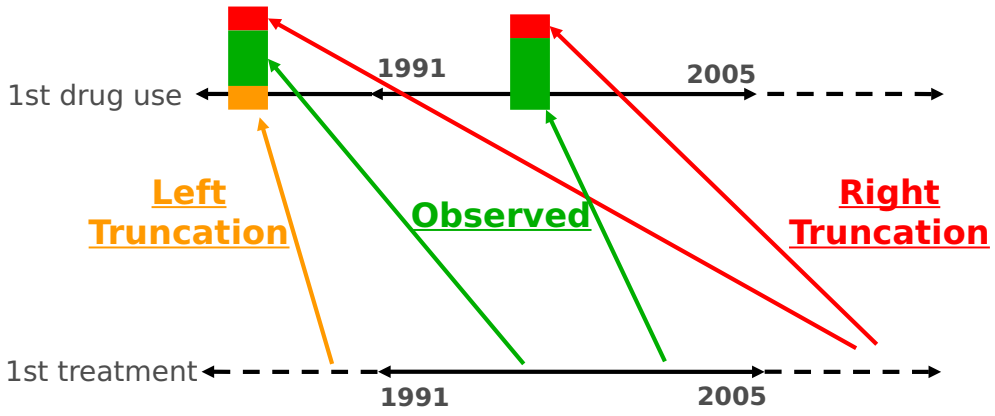

Figure 4.1: A graphical example of types of truncations.

Assuming independence in the observed cells, i.e. assuming quasi-independence, a log-linear model was used to estimate the row and column parameters and subsequently to calculate the expected frequencies of the complete table: the item of interest here being the expected row marginal, the actual estimated incidence.

Note that in the article the concept of "lag time" is termed "latency period". Nowadays, "lag time" is preferred because "latency period" seems more oriented

to the idea of a latent infection which eventually develops into disease (e.g. HIV to AIDS). Also, the term "reporting delay adjustment method" refers to the "lag-correction method", as already remarked in section 2.1.1.

An R package called *esindrug* has been created which is capable of estimating the incidence of drug use through the log-linear model of quasi-independence. The reference manual for this package can be found in the annex, section 9.2.

The following section presents the differences between this approach and the previous ones. Afterwards we will mention an important limitation: the independence between rows and columns. We propose the row-column (RC) association model as an extension to circumvent this limitation.

4.1.1 Motivation

The lag-correction method (section 2.1) had the limitation that the lag time distribution was conditioned to a maximum lag of time. This is the maximum length of time for which first treatment data has been observed. Therefore, incidence for drug users outside this time range could not be estimated. Moreover, drug users whose lag time was longer than that maximum lag time likewise could not be taken into account.

As mentioned in section 1.3.1, treatment registers started to collect information about first treatment in 1991, and the last observed year, when the article was written, was 2005. So, using the lag-correction method, incidence of heroin use could only be estimated in the period covering from 1991 to 2005. That is, only "right truncation" was dealt with. However, we have seen in section 1.2 that the heroin epidemic started in the 70's, and it would be interesting to know the incidence from that time onwards. Moreover, between 1991 and 2005 the maximum lag time is 15 years, which in principle might not be enough time to take into account some heroin users that had still not entered treatment for the first time by 2005. For these reasons we needed to go further.

Unlike the lag-correction method, back-calculation only requires aggregated data on first treatment and a lag time distribution, which need not be based on the same treatment data. This flexibility in the data requirements has some drawbacks: it entails more uncertainty and a possible bias if the lag time distribution used is not appropiate. For instance, in section 2.2, incidence results obtained using back-calculation were very different depending on the year of treatment data due to this phenomenon. Taking advantage of the fact that Spanish treatment data contains individual information, we wanted to go further.

Coming back to the lag-correction method, Brookmeyer and Liao provided another procedure for calculating the conditional lag-time distribution, through Poisson regression [62] instead of through adapting survival analysis. They claimed that the two computational methods produced identical numerical results. The (discretized) non-parametric estimates of the conditional lag time distribution (see section 2.1.2) coincide with the same distribution calculated from the "lag time" parameter in a Poisson regression for a contingency table.

Interestingly, Brookmeyer and Damiano formulate the statistical problem of lag times in terms of an incomplete multinomial distribution [61]. It is well-known that conditioning a vector of independent Poisson variables by its sum yields a multinomial vector. Next, this relation between distributions is shown adapting it to the two types of truncations (left and right).

Let T be a full table of frequencies n_{ij} where rows $i = 1, \ldots, I$ represent years of first drug use and columns $j = 1, \ldots, J$ represent lag time in years. J is the length of the interval from the first year of first drug use considered and the last observed year. Always $J \leq I$, otherwise T would contain empty columns. We consider T a square table, i.e. $J = I$ where J is the maximum feasible lag time.

We denote n_{ij} the cell count for row i and column j. Assuming $n_{ij} \sim Poisson(\lambda_{ij})$, where n_{ij} for all i and j are independent Poisson random variables, implies that the row totals $n_{i\cdot} \sim Poisson(\lambda_{i\cdot})$ where $\lambda_{i\cdot} = \sum_{j \in J} \lambda_{ij}$. Similarly, the column totals

$n_{\cdot j} \sim Poisson(\lambda_{\cdot j})$.

For the complete table T the independence hypothesis means that the matrix $\Lambda = (\lambda_{ij})$ has rank 1, or equivalently, that lag times are equally distributed across first drug use years (since all rows in Λ are proportional). Let λ_{ij} be the following functional form:

$$\lambda_{ij} = c \cdot a_i \cdot b_j \tag{4.1}$$

where c is a constant value, $\sum_{i=1}^{I} a_i = 1$ and $\sum_{j=1}^{J} b_j = 1$. We therefore have $\lambda_{i\cdot} = c \cdot a_i$ and $\lambda_{\cdot j} = c \cdot b_j$.

Denote by F this common cumulative distribution function and by f its probability mass function. Defining t as a continuous lag time, the discretized form of f is as follows:

$$f(j) = Prob\{t \in [j, j+1)\}. \tag{4.2}$$

The relationship between Poisson and multinomial distributions is that the vector $n_i = (n_{ij}, 1 \leq j \leq J)$, conditioned to the sum $n_{i\cdot} = \sum_{j=1}^{J} n_{ij}$ taking a fixed value $n^0_{i\cdot}$, is a multinomial vector with parameters $(n^0_{i\cdot}; f_i)$ where

$$f_i = \frac{\lambda_{ij}}{\lambda_{i\cdot}} \tag{4.3}$$

is a probability vector of length J.

If equation 4.1 is satisfied, then $\lambda_{i\cdot} = \sum_{j=1}^{J} \lambda_{ij} = c \cdot a_i$ and $f_i = \frac{\lambda_{ij}}{\lambda_{i\cdot}} = b_j$. Note that f does not depend of i, i.e. f is equally distributed for all i.

Now, let $S \subset T$ be the observed incomplete table. For each i, observed cells are those in an interval of columns $[J'(i), J''(i)]$, that is, we observe n^S_{ij} for $1 \leq J'(i) \leq j \leq J''(i) \leq J$. Figure 4.2 shows the structure of the observed cells.

Let $p_i(j)$ be the probability of observing a lag time in the interval $[j, j+1)$ for an individual starting drug use in year i, that is:

$$p_i(j) = Prob\{t \in [j, j+1) | j \in [J'(i), J''(i)]\} = \frac{f(j)}{\sum_{k \in [J'(i), J''(i)]} f(k)}. \tag{4.4}$$

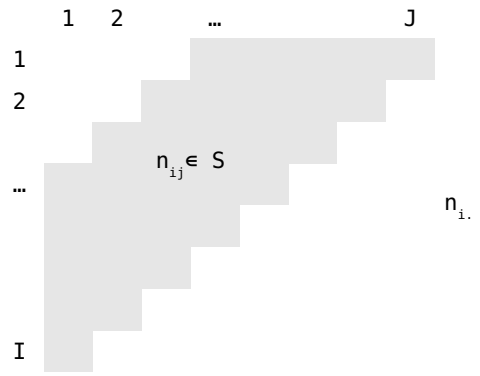

Figure 4.2: Incomplete table of frequencies. Note that $J''(1) = J$ and $J'(I) = 1$.

Row totals of table S,

$$n_{i\cdot}^S = \sum_{j \in [J'(i), J''(i)]} n_{ij}^S. \tag{4.5}$$

are obviously biased estimates of drug use incidences.

For each i, the observed counts n_{ij}^S, when conditioned on the total $n_{i\cdot}^S$, follow a multinomial distribution with sample size $n_{i\cdot}$ and probabilities $p_i(j)$.

For this incomplete table, in the same way as above, we relate the multinomial with the Poisson distribution but this time in terms of a truncated multinomial, i.e. the vector $n_i^S = (n_{ij}, J'(i) \leq j \leq J''(i))$, conditioned to the sum $n_{i\cdot}^S = \sum_{j=J'(i)}^{J''(i)} n_{ij}$ taking a fixed value $n_{i\cdot}^{S,0}$, is a multinomial vector with parameters $(n_{i\cdot}^{S,0}; p_i)$ where $p_i = (p_i(j); J'(i) \leq j \leq J''(i))$.

Estimates of $p_i(j)$ are:

$$\hat{p_i(j)} = \frac{n_{ij}^S}{n_{i\cdot}^S} \tag{4.6}$$

As we want to estimate parameters $f(j)$, we isolate these parameters from equation 4.4 as follows:

First we apply summation of k' from 1 to J:

$$\begin{aligned}
\sum_{k'=1}^{J} f(k') &= \sum_{k'=1}^{J} \left(p_i(k') \sum_{k=J'(i)}^{J''(i)} f(k) \right) \Rightarrow \\
1 &= \sum_{k'=J'(i)}^{J''(i)} p_i(k') \sum_{k=J'(i)}^{J''(i)} f(k) \Rightarrow \\
\frac{1}{\sum_{k=J'(i)}^{J''(i)} f(k)} &= \sum_{k'=J'(i)}^{J''(i)} p_i(k').
\end{aligned}$$

Then, replacing the above expression into terms of equation 4.4, we obtain $f(j)$ isolated:

$$f(j) = \frac{p_i(j)}{\sum_{k'=J'(i)}^{J''(i)} p_i(k')}, \quad j \in (J'(i), J''(i)). \tag{4.7}$$

Instead of estimating parameters $f(j)$ as above, they can be obtained using computing routines for Poisson regression by means of applying logarithms to the equation 4.1:

$$log(\lambda_{ij}) = \gamma + \alpha_i + \beta_j. \tag{4.8}$$

Details on how the parameters α_i and β_j can be estimated are found in the article.

Moreover, application of the Delta method to calculate the variability of incidence and lag-time probability estimates can be found in annex section 9.1.

4.1.2 Summary of results

Article 1 presents figures of incidence estimates of heroin use in general and by route of administration, injecting, smoking and snorting (figure 2 and 3, annex section 8.1). Note that route of administration refers to the most frequent route of heroin administration in the last 30 days before the treatment admission. Differences of incidence estimates by sex were commented on but not presented there; they can be viewed here in figure 4.3.

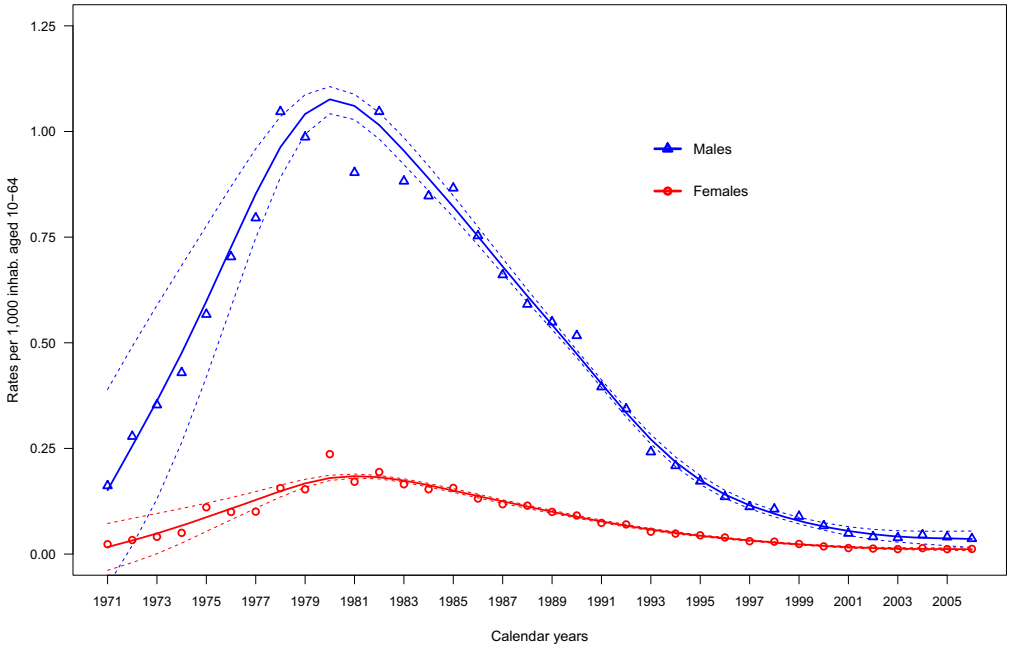

Figure 4.3: Estimates of incidence rates of heroin use by sex.

Overall the highest incidence estimates were situated around the year 1980, and decreased afterwards. Incidence of heroin use by injection followed a similar pattern, whereas that for smoking remained stable during the 80's. Therefore, these results seem to agree with our previous knowledge about the heroin epidemic, in that news about the increase of heroin users started in 1978, and indicators noted the decrease in the 90's (sections 1.2 and 1.3).

In addition, article 1 also presents the lag time distribution of heroin use in general and by route of administration (table 2, annex section 8.1). The median of lag time was around 3 years, and almost 90% of people started their first treatment in less than 10 years since their first use. So, it seems that heroin users, who eventually enter into treatment, require help relatively soon, particularly those who used injection compared to those who used smoking or snorting.

Article 1, figure 4, shows the different lag time distributions produced by different periods of years of treatment. The fact that treatment offer in Spain was

not stable over the years is discussed. Assuming stability of offer is equivalent to assuming lag time equidistribution, and in other words, to the assumption of quasi-independence between rows and columns of the incomplete table. The following section, contemplated after publication of the article, suggests a class of models that try to overcome this assumption of quasi-independence.

4.1.3 Row-Column association model

This class of models, known as row-column (RC) association models, were proposed by Goodman in 1979 [92], and their general form, called RC(M) is as follows:

$$\log(\lambda_{ij}) = \gamma + \alpha_i + \beta_j + \sum_{k=1}^{M} \phi_k u_{ik} v_{jk}, \quad i = 1, \ldots, I; j = 1, \ldots, J. \tag{4.9}$$

This model becomes saturated when $M = min(I-1, J-1)$. Parameter ϕ is the *intrinsic association*, while α_i and u_i represent row effects and, β_j and v_j column effects.

For simplicity, we studied the case of $M = 1$:

$$\log(\lambda_{ij}) = \gamma + \alpha_i + \beta_j + \phi u_i v_j, \quad i = 1, \ldots, I; j = 1, \ldots, J. \tag{4.10}$$

This model is not loglinear, because the predictor is a multiplicative function of parameters u_i and v_j.

Agresti warned that the RC model presents complications that do not occur with loglinear models [93]. The likelihood may not be concave and may have local maxima. Many authors have been developing approaches to estimate the parameters consistently [94, 95], and we have only found two software routines for fitting RC models: a Fortran program called **lspassoc** [96], and the **gnm** package for R [97]. Using these routines with the incomplete table of our article, led to convergence problems. For this reason, we attempted to estimate the parameters of our RC(1) model with a procedure developed in-house, that can be found in the annex 9.3. However, we continued to encounter convergence problems, so that

depending on the initial values we obtained different estimates. We attributed this problem to the incomplete table being too big and having too many empty cells.

4.1.4 General assessment

We have seen in section 1.2.4 that the National Plan on Drugs was created in 1985 and from that moment onwards more and more treatment centers progressively became available. It therefore makes no sense to say that people who started heroin use in (e.g.) 1975 would have a similar lag time distribution as people who started in 2000. People who started heroin use in 1975 and sought help before 1985 had to resort mostly to hospitals where the care provided for heroin dependence would have been different from that delivered later on, in the treatment centers. Therefore, assuming lag time equidistribution to estimate incidence in Spain since the 70's is not convenient.

The RC association model attempts to overcome this limitation. Nevertheless, we became aware that this approach, despite overcoming the convergence problems and obtaining valid estimates of incidence, has another problem: we considered only treatment data. As practically no treatment was available before the 90's, heroin users sought other forms of help (or died). So, incidence estimates for the 70's and 80's would also be infraestimated, as treatment data does not reflect the multitude of heroin users starting in those years. Therefore, the RC association model must be considered unable to produce reliable estimates for the incidence trend before the 90's.

Article 1 published the first approximation of incidence in Spain which approximately agreed with the historical events of heroin use, according to drug use experts. However, in the presence of these limitations we needed to go further and it seemed that the RC association model might not be the correct direction.

4.2 Article 2: The multi-state model

The second article, A multi-state model to estimate incidence of heroin use (annex section 8.2) deals with the same Spanish treatment data source as the previous article but incorporating one more year. Thus, records of first treatment cover from 1991 to 2006. In addition, external information on mortality and cessation rates related to heroin use was incorporated in a multi-state model.

There are plenty of studies in the literature involving multi-state models. For example, an early one is by Kalbfleisch and Lawless who mentioned the possibility of including mortality among HIV-infected patients, prior to their developing AIDS disease, even though they foresaw estimability problems [63]. Other studies using a similar idea include that by Aalen et al, coauthor of Article 2, where they described the progression from HIV infection to AIDS disease in several stages [98].

The present formulation of the multi-state model is the most basic as it was based on a Markov process, i.e. memoryless, and additionally assuming the probability of entering first treatment is independent of the time when the individual's drug use began. This could be a limitation, and for this reason, in section 4.2.3, we propose an extension to a semi-Markov model which was finally not applied in the article.

4.2.1 Motivation

The purpose of this article was to improve the estimation of heroin use incidence, obtained in the previous article, in two senses, by:

- taking into account a proportion of heroin users who never enter treatment, either because they die or permanently cease consumption, and
- avoiding imposing an explicit "a priori" lag time distribution which caused problems identified in the previous article (section 4.1).

Regarding the first point, the initial part of the trajectory of an heroin user was represented via three states (see figure 1 in the article): the initial state "heroin consumer" is followed by transition to either "entered first treatment" or to "left heroin use" (i.e. permanent cessation or death). The main aim was to estimate the number of individuals who made the transition to the initial state of "heroin consumer", that is incidence, taking into account the posterior transitions. Consequently, a standard Poisson type likelihood function was designed in accordance with the directions of these transitions and the type of data we had. See equations 1 and 2 of the article.

Regarding the second point, no explicit lag time pattern or functional form was imposed when constructing the likelihood function. As figure 5 in the article shows, the observed and expected lag time distributions for each cohort of heroin use onset fitted very well. So, as remarked in the article, modifying equation 1 to include the probability of entering first treatment, conditional on the initiation of heroin use, would have been too complex and of little practical importance.

We made assumptions about the transition rates of entering first treatment before year 1991 based on the history of heroin use in Spain. These are "educated assumptions", not supported by numerical evidence. For this reason, error terms were included in the transition rates and a sensitivity analysis was performed to contrast incidence differences.

4.2.2 Summary of results

Article 2 presents estimates of incidence rates in Spain, both overall and by route of administration (figure 2, annex section 8.2). Note that route of administration refers to the route of heroin administration used most frequently in the 30 day period prior to admission to treatment.

Briefly, the incidence rates were highest all through the 80's, being highest for injectors initially, and later highest for non-injectors. From the beginning of the 90's, incidence decreased very sharply. Therefore, these results seem to agree with

our previous knowledge of the Spanish heroin epidemic, described in the introduction.

The estimates of the probabilities of entering treatment for the first time, p_t, showed a general increase, even when incidence was decreasing. However, from 2002 onwards estimates were progressively more unstable. In particular the p_t estimate for 2006 was excessively high and its confidence interval too wide. For this reason, incidence and p_t estimates for 2006 were not included in our results. A possible explanation for this phenomenon is the small number of observations, mainly for injectors, in the last years observed.

Sensitivity analysis, based on 4 different combinations of parameter assumptions, presented the comparison of 4 curves of incidence estimates. These curves showed large variations in the eighties when incidence was highest (see figure 6 of article 2). Note that lower cessation and mortality rates yielded lower incidence rates, and vice versa.

4.2.3 A semi-Markov model

We have commented above that the observed and expected lag time distributions for each cohort of heroin use onset fitted very well. So, the assumption of independence from equation 1 could be considered adequate. However, the probability of entering first treatment might not be independent of the time of first drug use.

For that case, we discussed the possibility that the treatment probability p_t, which is a function of calendar time t, could also be a function of the lag time. For example a function such as that in the logistic model below could be used. Let s denote the lag time and let α_s and β_t denote the effects of lag time and calendar time respectively. The probability of treatment in a logistic model is then given by:

$$p_{st} = \frac{exp(\alpha_s + \beta_t)}{1 + exp(\alpha_s + \beta_t)} \tag{4.11}$$

Incorporating 4.11 in the equation (1) of the article, estimates could be more accurate. Therefore, this approach could be an alternative.

4.2.4 General assessment

Including mortality and cessation at least made it possible to account for almost all problematic heroin users. Incidence estimates correspond to our historical knowledge of heroin use in Spain.

The four results in the sensitivity analysis showed that different parameter assumptions made do not affect the conclusions. However, enhancing accuracy in the parameters could improve the estimates.

Although it has been possible to estimate incidence without needing to explicitly impose a lag time distribution, the instability of estimates for the last few years suggests the need for further model improvements.

4.3 Article 3: Standardizing the composite retrospective estimator

The third article "Incidence trends of cannabis and cocaine use from periodic Spanish general population surveys: effect of standardizing results by age structure" is based on the same approach as Gfroerer et al [86], explained in section 2.3. Methodologically speaking, this approach is quite straightforward. In fact we had already implemented it before discovering the 1992 publication by Gfroerer et al. Nevertheless, our contribution has been to re-visit this "old" approach, incorporating standardization of the incidence by the age structure of the population. This strategy may be an obvious one in epidemiological terms, but it might have been overlooked. By not considering such standardization in the analysis, the results can lead to wrong interpretations, as we emphasize in this article. This is important since recently many countries, like Spain, have begun to use periodic surveys, and their analysis should take into account the changing population age structure.

The strengths and weaknesses of this approach are mentioned in section 2.3. Here we will only focus on the methodological contribution: the standardization.

The article presents incidence estimates for general consumption of cannabis and cocaine in Spain as they are the most prevalent illegal substances in recent years. We used data from eight editions of the EDADES series of surveys (section 1.3.4) conducted between 1995 and 2009.

4.3.1 Motivation

Estimation of incidence of cannabis and cocaine use in Spain has been possible mainly for two reasons. Firstly, repetition of the same survey (or very similar) every two years has permitted obtaining more robust estimates of incidence trends, while possibly reducing biases (see section 2.3). Note that we worked with 8 surveys covering the 15 year period from 1995 to 2009. Secondly, the high prevalences in recent years help in achieving representativeness of the samples regarding use of

cannabis and cocaine ever (see section 1.3).

Standardization of the incidence estimates in Spain was a crucial point as the age structure of the population has changed over the years. Annex 1 of the article presents the population pyramids for the years 1995 and 2009. We can observe in figure A1 of the article that the proportion of young people (15 to 29 years old) decreased substantially. Seeing this, we realised that changes in the age structure of the population had to be controlled for when determining incidence.

4.3.2 Summary of results

The main results are shown in figure 1 of the article. Estimates of incidence rates of cannabis and cocaine use in Spain were represented in two graphics: one for raw rates and the second for standardized rates. We used the term "raw" to differentiate from "standardized". Raw incidence rates are valid estimates for each year, but they should not be compared between years, i.e. considering their trend in the graph can lead to wrong conclusions. For this reason standardized rates, in our case adjusted by the population age structure for the year 2008 (any year could be used as the reference), are more suitable for representing trends.

The increase of cannabis and cocaine use incidence in the 90's corresponds to the change of pattern from heroin use to other drugs like cannabis and cocaine (see section 1.2).

Other interesting results are revealed in figure 2 where the group aged 15 to 19 years had the highest incidence rates for both substances and both genders. Interestingly, incidence of cannabis use in people younger than 15 years increased in the 90's. These results highlight the need to increase efforts in preventing cannabis use in the population long before the age of 15.

4.3.3 General assessment

Incidence figures can be underestimated due to the numerous limitations and biases explained in the discussion section of the article. However, as in previous methods, taking account of incidence trends, rather than levels, is preferred as they reliably indicate the direction of the epidemic.

Part III

Discussion

Torture the data long enough and they will confess to anything.

Anonymous

CHAPTER

5

Comparison of results

Three methods have been developed to estimate incidence of drug use in Spain. Article 1 estimated incidence of heroin use using the loglinear model of quasi-independence (LLM), article 2 also estimated incidence of heroin use but using the multi-state model (MSM), and article 3 estimated incidence of cannabis and cocaine use using the standardized composite retrospective estimator (SCRE).

The aim of this chapter is to make a direct comparison of the incidence results between the methods according to the substances and make clearer their suitability. In addition to the LLM, MSM and SCRE, the lag-correction method has also been included in the comparison to show how it differs from the LLM, since these two approaches are similar, depending on the substance. On the other hand, the MSM was not used for cocaine and cannabis due to the lack of information about mortality and cessation.

The following sections present the incidence estimates by substance. All incidence results were re-estimated for ages from 10 to 64, to make the comparison feasible.

5.1 Incidence estimates of heroin use

Figure 5.1 presents four incidence estimates of heroin use in Spain where the points are the estimates and the curves are their weighted cubic smoothing splines in order to extract smoothed fitted trends and their 95% confidence intervals. The methods are the following:

- The log-linear model of quasi-independence (LLM).
  - Data sources are treatment registers (entries to treatment for the first time between 1991 and 2006).
  - Estimates can be found in Article 1.
- The multi-state model (MSM).
  - Data sources are the same treatment registers, plus mortality and cessation rates.
  - Estimates can be found in Article 2.
- The lag-correction method (LCM).
  - Data sources are the same treatment registers.
  - Estimates have not been presented anywhere else.
- The standardization of the composite retrospective estimator (SCRE).
  - Data sources are the biennial EDADES surveys between 1995 to 2009.
  - Standardization: the year of reference is 2008.
  - Estimates have not been presented anywhere else.

Concerning these incidence curves based on treatment data, we may observe that:

- Firstly, the most remarkable difference is that, according to the LLM, incidence was highest around 1980 whereas according to the MSM it was highest between 1985 and 1990. Certain biases may be inherent in the assumptions made

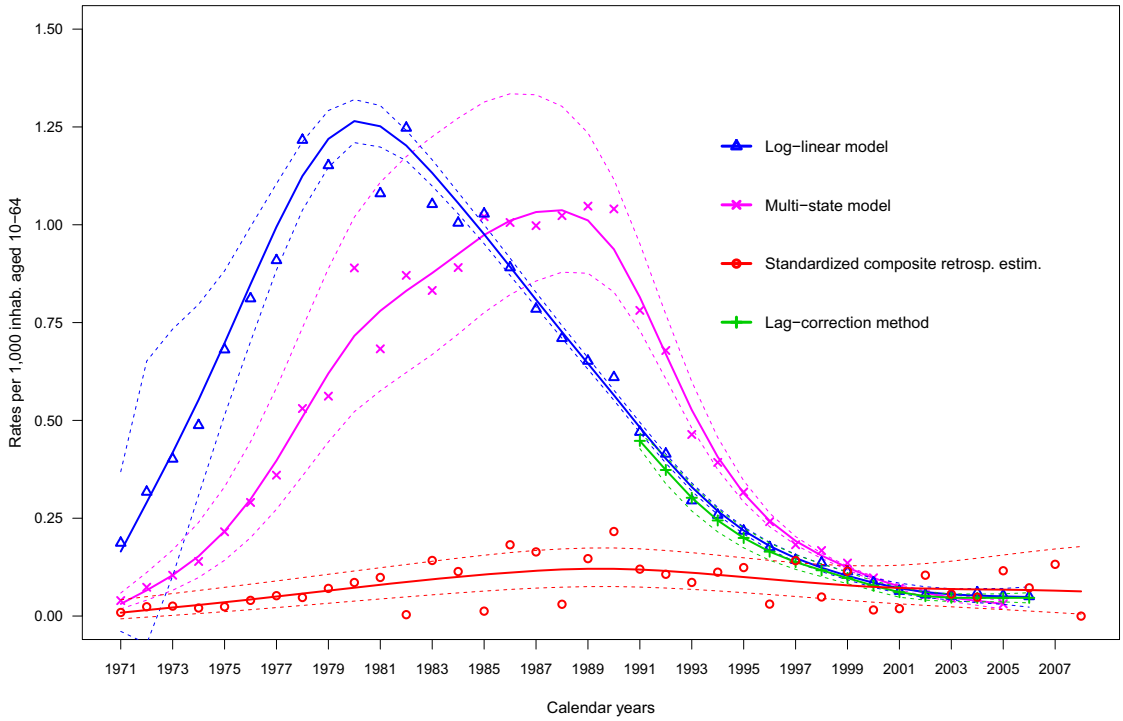

Figure 5.1: Incidence estimates of heroin use by method.

by these two methods, although the direction of such bias cannot be determined. The LLM assumes that treatment offer was stable over the years, which we know is not correct. In addition, the peak of incidence in 1980, yielded by the LLM, seems sooner than expected. Therefore, regarding the trend of incidence estimation of heroin use in Spain, MSM results appear to be more appropriate than those of the LLM, at least before the 90's.

- Secondly, incidence estimates yielded by the MSM fell steadily and were below those by the LLM and LCM from 2001 onwards. Again, the direction of bias cannot be determined and so it is difficult to assert which is more adequate. However, estimates by the MSM in the last few years were unstable (see section 4.2). On the other hand, more consistent estimates can be achieved using both the LLM and the LCM if the lag time distribution adopted is appropriate for these last years.

- Thirdly, estimates produced by the LLM and LCM methods were similar for the period from 1991 to 2006. This is explained because their lag time distributions are similar due to the short length of time that most of heroin users delay their entry to treatment for the first time (a median of around 2-3 years).

Concerning the incidence curve estimated by the SCRE, we see that it is generally much lower than the other estimates, and although slightly higher from 2002 onwards, this is not relevant given the wide variability of the estimates in the last few years. As has been mentioned in previous sections (see for example section 2.3.1) survey data tends not to be suitable for estimating incidence of heroin use because these users are difficult to reach at home, and the stigma associated with this substance may mean users have greater fear of disclosure than those of other illegal substances such as cannabis or cocaine.

5.2 Incidence estimates of cocaine use

Figure 5.2 presents three incidence estimates of cocaine use in Spain where the points are the estimates and the curves are their weighted cubic smoothing splines in order to extract smoothed fitted trends and their 95% confidence intervals. The following methods have been taken into account:

- The standardization of the composite retrospective estimator (SCRE).
  - Data sources are the biennial EDADES surveys from 1995 to 2009.
  - Standardization: the year of reference is 2008.
  - Estimates can be found in Article 3.
- The log-linear model of quasi-independence (LLM).
  - Data sources are treatment registers (entries to treatment for the first time between 1991 and 2006).
  - Estimates have not been presented anywhere else.
- The lag-correction method (LCM).
  - Data sources are the same treatment registers.
  - Estimates have not been presented anywhere else.

In contrast to incidence estimates of heroin use, estimates of cocaine use yielded by the LLM and LCM have very different magnitudes, even though they have approximately similar trends. This difference arises because the lag times between onset of use and start of treatment among cocaine users are much longer. Using the LLM, a lag time distribution with a median of around 24 years was estimated. On the other hand, using the LCM, the lag time distribution had to be conditioned to a maximum of 16 years, due to methodological restrictions. I.e., the median of the LLM's lag time distribution was higher than the LCM's maximum lag time length.

As in the case of heroin, the LLM assumes lag time equidistribution, i.e. that treatment offer was stable throughout the time period involved, an assumption we

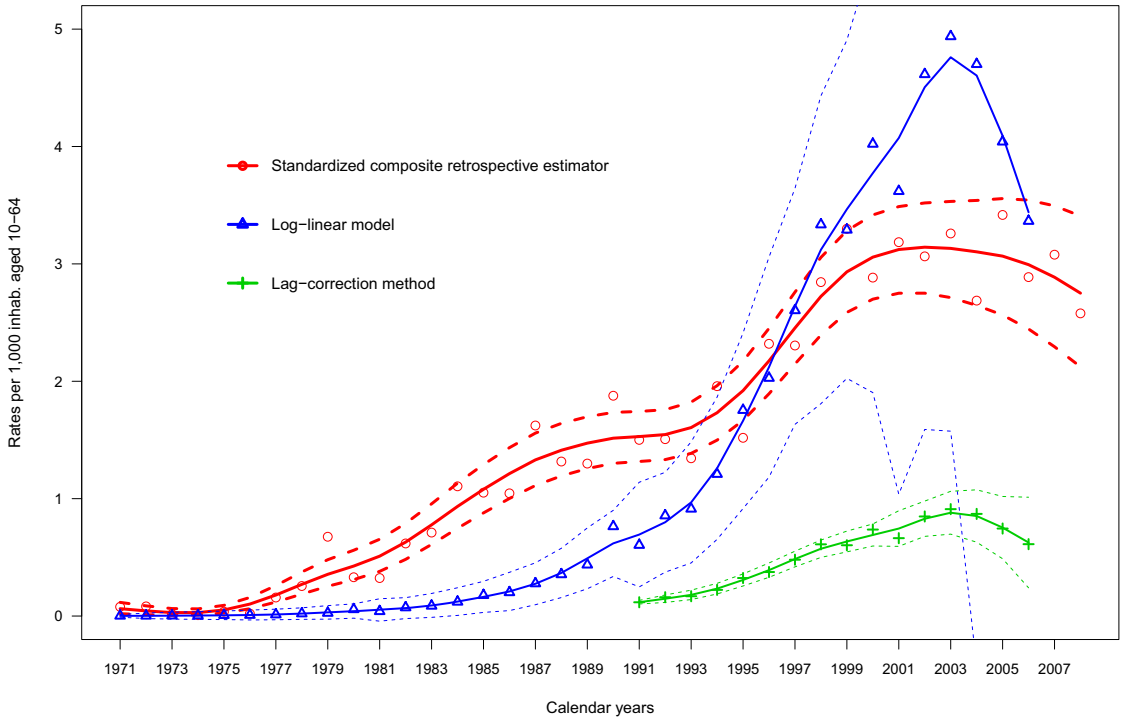

Figure 5.2: Incidence estimates of cocaine use by method.

know is not appropriate. So, the long lag times may be attributed to the scarce availability of treatment before the 90's. In addition, the combination of the fact that treatment demand rose during the observed period of years, and the long lag times, accounts for both the rising incidence trend and the very high variability, as people who initiate cocaine use at some point in the last few years observed are expected to enter their first treatment a median of 24 years later.

Therefore, neither of the two methods can be considered to provide reliable incidence estimates at the moment. Estimates may be expected to improve considerably by using longer series of observed treatment data.

Incidence estimates using the SCRE show an initial sharp rise in the early 80's that is not reflected in the other incidence estimates. On the other hand, the second sharp rise from 1995 to 2000 is reflected in the other estimates, although of a

slightly shorter duration. Interestingly, all three curves show a (non-significant) decreasing trend from 2003 onwards.

As incidence estimates from survey data may involve both problematic and non-problematic users, they are likely to be higher than incidence estimates from treatment data. This was the situation up until the 1997, and although subsequently this situation appears to be reversed, differences in the estimates were non-significant.

It would be very interesting to know the proportion of people who have ever entered treatment out of those who have ever used cocaine. Unfortunately, this information has not been collected in Spanish surveys.

5.3 Incidence estimates of cannabis use

Figure 5.3 presents three incidence estimates of cannabis use in Spain where the points are the estimates and the curves are their weighted cubic smoothing splines in order to extract smoothed fitted trends and their 95% confidence intervals. As in the case of cocaine, above, the following methods have been taken into account:

- The standardization of the composite retrospective estimator (SCRE).
  - Data sources are the biennial EDADES surveys between 1995 to 2009.
  - Standardization: year of reference is 2008.
  - Estimates can be found in Article 3.
- The log-linear model of quasi-independence (LLM).
  - Data sources are treatment registers (entries to treatment for the first time between 1996 and 2006).
  - Estimates have not been presented anywhere else.
- The lag-correction method (LCM).
  - Data sources are the same treatment registers.
  - Estimates have not been presented anywhere else.

The difference in the magnitude of incidence estimates between those using methods based on treatment data and that using the SCRE with survey data is noteworthy. Note that treatment data refers to people entering treatment for cannabis consumption as a first cause. As people consuming only cannabis have a relatively low risk of needing treatment for dependence problems, in contrast with individuals who consume substances like heroin or cocaine, their proportion with respect to the total of persons having ever used is expected to be very low.

Incidence estimation of cannabis use from treatment data may be of interest in order to monitor trends of problematic users. However, as happens with cocaine, lag times between onset of use and the start of first treatment may be longer than

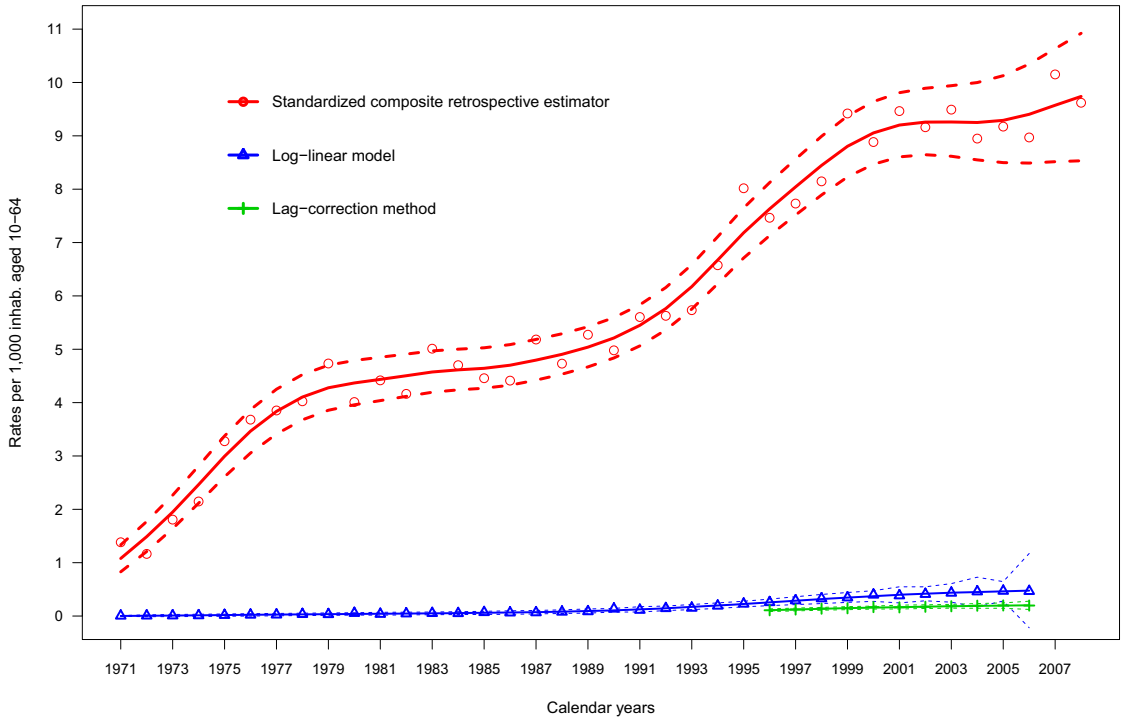

Figure 5.3: Incidence estimates of cannabis use by method.

the span of observed years, leading to the loss of an appreciable proportion of consumers who could in the future become problematic cannabis consumers.

Drug epidemics eventually die when new cohorts observe the drug's ill-effects on their seniors.

Musto

CHAPTER

6

Conclusions

- The incidence trends for heroin, cocaine and cannabis use estimated in this work agree with our knowledge of the history of illicit drug use epidemics in Spain.
- The multi-state model (MSM) appears to be the method yielding the most accurate estimates for incidence of heroin use in Spain, at least prior to 2000. On the other hand, incidence estimation for the most recently observed years should rely on some method supported by a lag time distribution, such as the log-linear model (LLM) or lag-correction method (LCM).
- Heroin use incidence figures estimated by the MSM take into account at least all those individuals whose consumption became problematic. We do not know whether the cessation rate used in our model included non-problematic users.
- Heroin use incidence estimates, yielded by the standardized composite retrospective estimator (SCRE) approach using general population surveys, are not valid, mainly because consumers are usually difficult to reach due to heroin being a stigmatized substance. Moreover, the Spanish EDADES series of population surveys started after the heroin epidemic phase.

- The SCRE approach probably provides more accurate incidence estimates of cocaine use in Spain than methods based only on treatment data.
- The estimates of cannabis use incidence in Spain yielded by the SCRE approach are clearly much more accurate.
- The SCRE approach, through using general population surveys, tends to produce estimates of incidence for non-problematic drug users, rather than problematic ones.
- Incidence *trends* may be assumed to be more reliable than their *magnitudes*, providing the proportion of unknown drug users remains stable.
- The histories of drug use incidence trends in Spain have been assessed. However, incidence estimates cannot usually be performed until between 2 and 5 years after collection of treatment or survey data is completed. The usefulness of such estimates for preventive health policies and evaluation of interventions is therefore limited.

My love of dynamic complications often led me to avoid simplicity when perhaps it was the wisest choice.

Garry Kasparov

CHAPTER

7

Future research

There are two directions in which to continue the line of research into drug use incidence. One is to improve on the methods presented here, for example by exploring approaches such as the row-column association model (section 4.1.3), the semi-Markov model (section 4.2.3), and a parametric approach to the lag-correction method presented in the next section 7.1.

A second, more ambitious, line of research, presented below in section 7.2, goes further by focusing on drug user's careers. An important limitation, to be addressed in more detail in the conclusions, arises because usually it is not possible to make incidence estimations before a considerable length of time has elapsed since the moment when data were obtained. This delay means that such estimates may not be particularly useful for evaluation and prevention in current health policies. For this reason, the following proposal endeavors to study drug user's careers. In statistical terms, the drug user's career is modelled as a framework of related compartments which capture its dynamics. This kind of dynamic model can predict trends by means of "what if" scenario analysis, and thus may provide more useful information for policy makers.

7.1 Parametric approach to the lag-correction method

The lag correction method is based on estimating a non-parametric lag time distribution. However, as we have seen in the Spanish context on assuming quasi-independence, the problem is that lag times are assumed equidistributed for each year of first drug use. So, the idea would be to consider a lag time distribution which changes over time, taking into account that each cohort of year of first drug use is right-truncated with a different maximum observed lag time. As this distribution usually follows a similar pattern, a practical option would be to consider resorting to a known parametric family of distributions. We have seen that the back-calculation method considered that the Weibull distribution seemed to fit the lag times in heroin users fairly well (see section 2.2).

We therefore consider that the lag time distribution follows a *truncated Weibull distribution* $F_i(x)$ and fit one such distribution to each cohort of year of first drug use i. Let X be a random variable representing the truncated distribution over the interval $[a_i, b_i]$. The probability density function is given by

$$f_i(x) = \begin{cases} \frac{g(x)}{G(b_i)-G(a_i)} & \text{if } a_i \leq x \leq b_i \\ 0 & otherwise \end{cases}$$

where we have a non-truncated Weibull distribution specified by $G(\cdot)$ and probability mass function $g(\cdot)$.

The approach and some initial results were presented in the congress on biostatistics (ISCB Bergen 2012), even though further development is required [99].

7.2 Dynamic models

Policy makers need information to describe and understand the situations involving problematic drug consumption, follow trends over time, design appropriate interventions and evaluate the results of actions taken. However, the information available is complex because it consists mainly of observational data and epidemiological indicators [100]. There have been similar studies trying to represent the spread of drug use in the population by dynamic models: in the United States, for heroin [101] and cocaine [102, 103]; in Australia for multiple drugs [104]; and in Germany for heroin [105]. Hilton et al pointed out that there is a lack of long-term longitudinal studies needed to inform dynamic models, because such follow-up studies are difficult, costly and time consuming [106].

Interestingly, Rossi implemented an operational model which uses macro indicators and can be used to generate estimates where data are sparse or to verify hypotheses or predict trends by means of "what if" scenario analyses [107, 108]. Besides, an European project team, also led by Rossi, studying drug policy evaluation (JUST/2010/DPIP/AG/1410) had as one of its goals to employ operational models and perform suitable scenarios to assess the impact of possible interventions, and has recently published a paper with an example involving cocaine users [109].

For example, the multi-state model of Article 2 can be treated as a dynamic model as the transitions between the states involve time. Figure 7.1 is similar to Figure 1 of Article 2, where $S(t)$, $D(t)$, $C(t)$ and $L(t)$ represent the prevalences in each state at time t, and h_t, p_t and q_t are the transition rates between those states.

An overview of the "diffusion" of heroin users between these states can be obtained by applying Markov models. In a Markov model the duration in each state is exponentially distributed. For example, a set of deterministic equations in discrete time t would be the following:

$$D(t+1) = D(t)(1 - p_t - q_t) + S(t)h_t$$

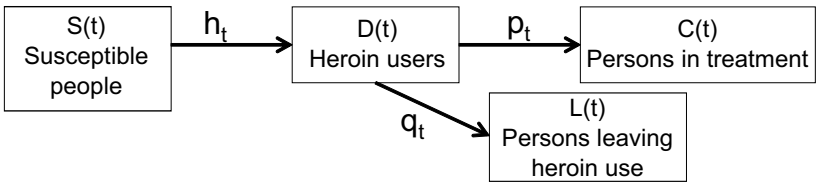

Figure 7.1: Multi-state model diagram. Parameter h_t denotes immigration of individuals starting heroin use, p_t transition rate entering treatment for the first time, and q_t transition rate leaving heroin use without entering treatment, at time t.

$$C(t+1) = C(t) + D(t)p_t$$

$$L(t+1) = L(t) + D(t)q_t$$

Note that the incidence rate of heroin use is h_t and the probability of entering first treatment is p_t. These differential equations can be solved numerically [109, 110]. This model can be extended including more compartments and dependences between compartments.

Attempts to go beyond Rossi's approach may require using semi-Markov and non-homogeneous models where future evolution not only depends on the current state but also on the entry time to that state. Also stochasticity can be included in the model equations. Moreover, to perform scenario analysis, different interventions should be assessed within the compartmental model. Dynamic path analysis can be used as a tool for assessing these interventions. Since causal modelling has gained importance in recent years, a causal point of view could be adopted by making use of mathematically more appropriate formulations of pathways to help us understand how things come about or why they happen [111].

This line of research, a natural development of studies carried out to the present moment, might be the threshold to a wider outlook on drug use epidemiology, transcending a mere incidence estimation.

Part IV

Annexes

But in science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs.

Sir Francis Darwin

CHAPTER

8

Published Articles

8.1 Article 1: Problematic heroin use incidence trends in Spain

Addiction
RESEARCH REPORT
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Problematic heroin use incidence trends in Spain

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ABSTRACT

Aims To estimate the annual incidence of heroin use in Spain. **Participants and design** Data on individuals' year of first heroin use (from 1971 to 2005), year of first heroin treatment between 1991 and 2005 and most frequent route of heroin administration when presenting to treatment were obtained from the Spanish Drug Observatory Register and used to calculate the delay between onset and treatment. By using a log-linear model approach it was possible to correct for missing observations (heroin users who presented for treatment before 1991 and those who had still not presented by the end of 2005) and to estimate heroin incidence over time. **Findings** The estimated incidence of problematic heroin use in the population aged 15–44 peaked at 190 per 100 000 in 1980—after rising rapidly from less than 40 per 100 000 in 1971—and fell subsequently to about 8 per 100 000 in 2005. On average, incidence was five times higher in men. Injecting heroin incidence peaked and declined rapidly from 1980; as heroin smoking did not decline as rapidly, from 1985 onwards its estimated incidence has remained above that of heroin injecting. The delay between starting heroin use and entering treatment had a median of 3 years. **Conclusions** We demonstrate the utility of a method to estimate heroin incidence from analysis of observed trends in presentations at specialist drug treatment facilities. The estimates suggest that incidence of heroin use, especially injecting, has fallen since 1980 and is now lower than in the early 1970s.

Keywords Epidemiology, heroin, incidence, latency period, log-linear model, route of administration.

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INTRODUCTION

Epidemiological measures such as prevalence and incidence provide information about health needs, useful for health care planning. Although approximate figures of both prevalence and incidence of drug abuse and dependence can be estimated through general population surveys [1], they can be difficult to assess reliably due to the hidden nature of illicit substances use and other survey limitations.

In Spain, heroin has generated important health problems in the last two decades [2]. According to treatment admissions, hospital emergencies and deaths related directly to drug use—the main indicators used by the Spanish Drug Observatory (SDO)—the highest problematic heroin use prevalence probably happened during 1987–92 and appears to have been decreasing since [3]. Attempts to estimate prevalence have used various methods, among which indirect methods [4] and capture–recapture [5] are probably the most common. At a European level there is growing interest in incidence estimation [6], as its trend can be extremely informative about epidemic dynamics and help to evaluate the adequacy of actions taken. However, methods for estimating incidence of drug use are not yet well established.

Hickman and colleagues [7] adapted the 'reporting delay adjustment' (RDA) method, devised by Brookmeyer [8,9] in the field of acquired immune deficiency disorder (AIDS) epidemiology, to estimate the incidence of heroin use in south-eastern England. They considered that the time interval between 'AIDS diagnosis' and 'AIDS reports' is analogous to the interval between 'onset of drug use' and 'treatment admission', known as the latency period (LP). Neither of these two cases reaches all subjects and

so, if not corrected, they result in an underestimated incidence caused by delay in reaching information systems, which in the case of drug use is due to the existence of users who had still not been admitted into treatment at the time of observation. As Hickman [7] discussed, the length of time during which treatment admissions are observed is very important. If this interval is long enough, the incidence estimated through RDA may approach population values, relative to individuals who have entered treatment at some point. However, in treatment admission registers the length of time available is often too short, so heroin users who take longer to be admitted escape the analysis because the maximum LP in RDA is equal to the length of the period observed [7]. Allowing the year of first heroin use to be earlier than the beginning of the period actually observed by the treatment admission register, something for which the RDA method provides no solution, means that a longer LP can be contemplated and that far more subjects can be included in the analysis.

Brookmeyer *et al.* [8] had already suggested that Poisson regression might be an alternative method to RDA. In fact, it provides the same LP distribution when data are conditioned to the same individuals [9], therefore it is easy to demonstrate that incidence results are identical. However, they recognized that the large number of parameters to be estimated could pose a problem, and also that the database used should be large enough. They considered that RDA seemed easier to work with. However, in contrast to RDA, Poisson regression does not restrict estimates to years within the observed period nor the length of the LP [10].

To develop this methodology further, the aim of the present analysis was to estimate the annual incidence of problematic heroin use in Spain between 1971 and 2005 by using log-linear models as a generalization of the Poisson regression method.

MATERIAL AND METHODS

The data

As in any country with universal health coverage, the Spanish drug treatment system is mainly public or publicly funded, and most patients entering treatment for drug dependence are screened in specialized out-patient treatment centres before being assigned a treatment modality, which may include in-patient treatment. Each autonomous community (Region) has its own treatment system organization. The SDO collects information about drugs from all the Spanish Regions, its basic function being to evaluate the situation of drug problems in the country. Data on drug treatment admissions, an indirect indicator of drug use, come from all public and publicly funded out-patient centres (initially 250, now some 500) in the whole country since 1987, and is available in a large database which includes socio-demographic information and drug profile. Double-counting is avoided at regional level with a confidential personal code. The quality of this indirect indicator of drug use was assessed in 1988 [11] and has been providing relevant information since then [12,13].

From that indicator, we selected for this study treatment admissions between 1991 and 2005, as prior to 1991 the registry did not collect, with a specific item, whether or not a treatment admission was reported by the patient as the first treatment ever. We were only interested in first ever treatment admissions. We obtained subjects from this database who were aged 10–44 years when they began heroin use, and 15–54 years when admitted for their first heroin treatment ever. These age restrictions, in order to avoid misleading values, occasioned a loss of 1.3% from the total. Year of onset of heroin use was restricted to the period from 1971 to 2005. There were isolated cases in years before 1971 (<0.5%) that were removed to ensure stability in the statistical modelling. In total, 167 753 individuals were analysed.

The most important variable was the reported year of heroin use onset. LP length was defined as the delay from this first heroin use to the treatment admission date reported as first. Other variables used in the analysis were gender and most frequent route of heroin administration in the last 30 days before that treatment admission.

Statistical methodology

Year of heroin use onset was cross-tabulated against LP length (in years); see Fig. 1. Attention is drawn to the two subsets of empty cells, resulting from truncations: left truncation, affecting people admitted to their first treatment prior to 1991, the first year observed; and right truncation, affecting people still not admitted into treatment by 2005. Because of these empty cells the row totals of the observed table, which provide the observed incidence, are not reflecting the real incidence correctly: we would need the full frequency table. Therefore, the proposal is to estimate the full table by means of an extension of a log-linear quasi-independence model (see equation 3 below) adjusted to the observed data. The row totals of the resulting table will constitute the estimated incidence (see equation 5 below).

Let T be the full table of frequencies f_{ij}, where $_i = 1, \ldots, I$ and $_j = 1, \ldots, J$, resulting from cross-tabulation of onset years and the years of LP, and let $S \subset T$ be the observed (incomplete) table. Equation 1 gives the cumulative sums of each ith row of the observed table, while equation 2 gives the cumulative sums of each jth column.

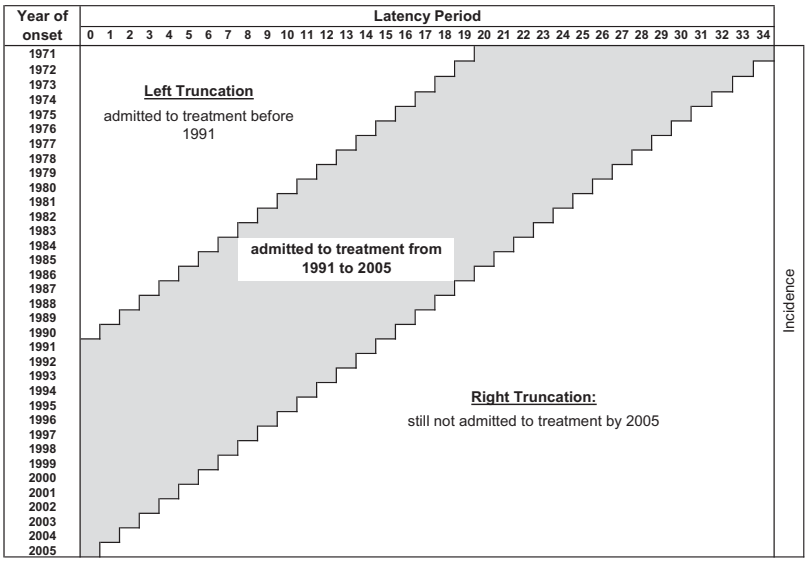

Figure 1 Table of frequencies with observed cells from people who were admitted to heroin treatment from 1991 to 2005

$$f_{i\cdot} = \sum_{j:(i,j)\in S} f_{ij} \qquad \text{(eqn 1)}$$

$$f_{\cdot j} = \sum_{i:(i,j)\in S} f_{ij} \qquad \text{(eqn 2)}$$

We employed the following log-linear model:

$$\log(m_{ij}) = \mu + \alpha_i + \beta_j, \quad \forall (i,j) \in S, \qquad \text{(eqn 3)}$$

where m_{ij} was the expected value of the cell (i,j), μ the mean of the model, αi the parameter representing row i and βj the parameter representing column j. In equation 3 independence is assumed only for cells from $S \subset T$. Such models are called quasi-independence models [14,15].

The software used for the statistical analysis was R version 2.7.1 [16]. Three models were assessed: Poisson, negative binomial and quasi-Poisson model, all with log-link and treatment contrast with baseline in the first level. We found that the Poisson distribution fitted better than the negative binomial (χ^2 Poisson: 6543; χ^2 negative binomial: 8437). In order to adjust for overdispersion we used the quasi-Poisson model (dispersion parameter: 18.6), whose parameter estimates coincided with those of the Poisson model.

The iteratively reweighted least squares technique (IRLS) was used to estimate the parameters of the model and, once performed, the expected value of each cell of the table was calculated as:

$$\hat{m}_{ij} = \exp\left(\hat{\mu} + \hat{\alpha}_i + \hat{\beta}_j\right), \quad \forall (i,j) \in T. \qquad \text{(eqn 4)}$$

Note that the estimation method allows us to extrapolate for unobserved cells. The resulting table is algebraically equivalent to an independence one for the general population, while in fact it has been obtained by fitting a quasi-independence model for the incomplete table actually observed. Lacking a more sophisticated alternative, this implicit assumption of independence seems reasonable.

The estimated incidence values were calculated as:

$$\hat{X}_i = \sum_{j:(i,j)\in T} \hat{m}_{ij}. \qquad \text{(eqn 5)}$$

The variance of the estimated parameters μ, αi and βj and that of the estimated incidence values were computed through the Delta method, a standard procedure for estimating variances of parametric functions [15].

Simultaneously, the distribution of LP was calculated in an analogous way:

$$\hat{F}(j) = \sum_{h\le j}\left(\sum_{i:(i,h)\in T} \hat{m}_{ih} \Big/ \hat{M}\right), \quad \text{where } \hat{M} = \sum_{(i,j)\in T} \hat{m}_{ij}. \qquad \text{(eqn 6)}$$

The standard errors of $\hat{F}(j)$ were also calculated with the Delta method. The distribution of LP (equation 6) offers the cumulative probabilities of delay between onset of heroin use and the first treatment episode. Therefore, it represents the percentage of people who started their first treatment before j years.

The observed and estimated incidences were converted to population rates for ages ranging from 10 to 44 years, based on yearly population census estimates extracted from the website of the Spanish National Statistics Institute [17]. The rates were smoothed with cubic splines to present the graphics as continuous curves.

In order to compare incidences between different categories of gender and route of administration, we stratified the data and analysed each category separately in the same manner.

RESULTS

Table 1 presents a descriptive analysis of the available variables. The mean age of onset was 21 years, and that

Table 1 Descriptive analysis of people admitted to treatment for heroin as the main drug for the first time in their life in treatment centres in Spain between 1991 and 2005.

	Female		*Male*		*Missing*		*Total*			
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	χ^2, t[a]	*P-value*
Total admitted to treatment	26 571	15.9%	140 788	83.9%	394	0.2%	167 753	100%		
Route of administration										
Injecting	7 264	27.3%	41 468	29.5%	143	36.3%	48 875	29.1%	705.02	<0.01
Smoking	15 584	58.7%	85 673	60.8%	189	48%	101 446	60.5%		
Snorting	2 588	9.7%	7 738	5.5%	38	9.6%	10 364	6.2%		
Other/missing	1 135	4.3%	5 909	4.2%	24	6.1%	7 068	4.2%		
Age of first use (mean ± SD)	21.4	(5.78)	21.2	(5.57)	20.7	(5.48)	21.2	(5.61)	3.82	<0.01
Age of first treatment (mean ± SD)	27.6	(6.43)	28.5	(6.54)	29.2	(5.96)	28.3	(6.53)	−20.27	<0.01

[a]Excluding cases with gender missing. SD: standard deviation.

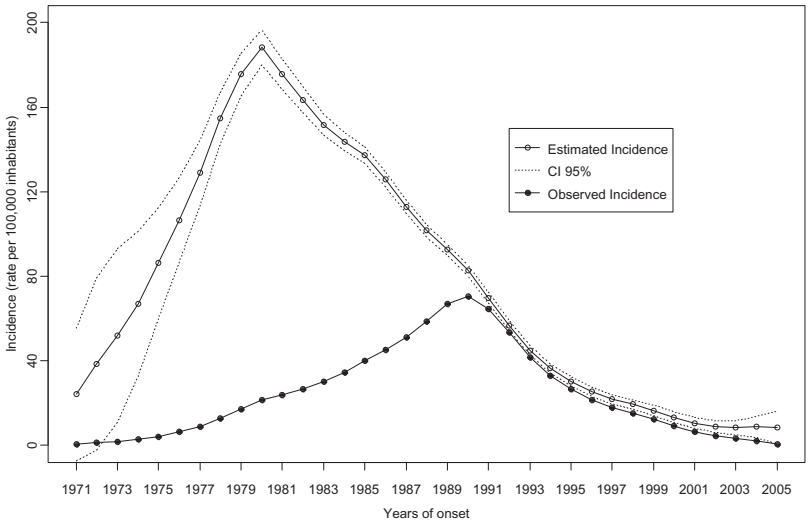

Figure 2 Observed and estimated problematic heroin use incidence rates* in Spain with 95% confidence interval. *Estimated incidences are relative to ever entering treatment

of first treatment was 28. In terms of gender, males predominated (84%), sex differences in age of onset and first treatment being significant. Smoking was the most frequent route of heroin administration in the 30 days before admission to treatment (60.5%), followed by injection (29.1%) and snorting (6.2%). In women, snorting was more frequent (9.7%) than in men (5.5%).

Figure 2 shows the observed and estimated incidence curves, all smoothed and converted to rates for ages 10–44 years. The observed incidence rates from available treatment data increased slowly until 1990, when the rate was approximately 70 per 100 000 inhabitants, dropping gradually afterwards. Based on these observed data, the estimated incidence rates of problematic heroin use increased rapidly during the 1970s, from less than 40 new users per 100 000 inhabitants in 1971, until 1980 when 190 new problematic heroin users per 100 000 inhabitants per year were estimated. After that, incidence decreased steeply until the mid-1990s, 30 new users per 100 000 inhabitants being estimated for 1995, then more slowly until 2002, having remained practically stable since then at approximately eight per 100 000 inhabitants.

The incidences estimated for men were higher than for women (for example, rates per 100 000 inhabitants in 1980 were: males, 316; females, 55), although showing similar trends (data not shown). Regarding route of administration (Fig. 3), estimated incidence for injection reached a peak of approximately 150 per 100 000 inhabitants in 1980 and then decreased rapidly, whereas that for smoking did not show such a prominent peak, but maintained its higher level throughout the 1980s at approximately 60 per 100 000 inhabitants. Although in the final years injection seems to have disappeared, the decrease of smoking is less and appears to be stable from

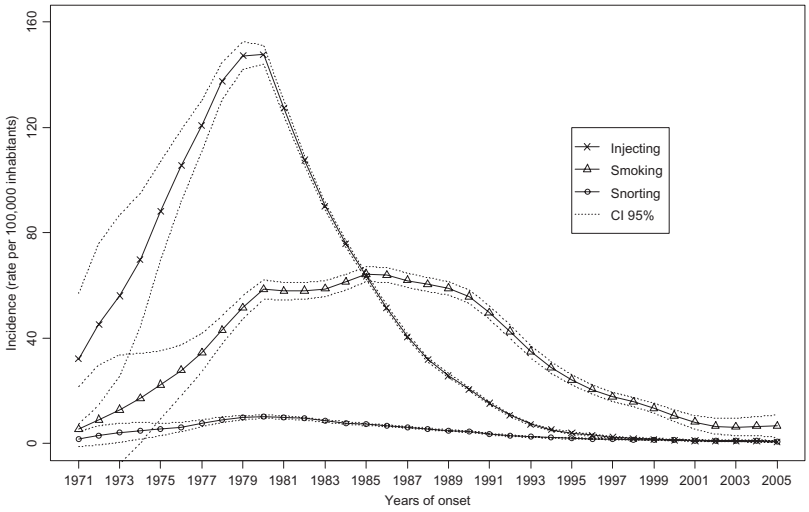

Figure 3 Estimated incidence rates* of problematic heroin use and their 95% confidence interval by route of administration reported at first treatment in Spain. *Estimated incidences are relative to ever entering treatment

Table 2 Latency period (LP) distributions from global data and stratified by route of administration.

		Route of administration		
Years of LP	*Global (SE)*	*Injecting (SE)*	*Smoking (SE)*	*Snorting (SE)*
0	0.06 (0.0034)	0.07 (0.0005)	0.06 (0.0006)	0.07 (0.0007)
1	0.24 (0.0056)	0.24 (0.0008)	0.23 (0.0009)	0.23 (0.0011)
2	0.39 (0.0074)	0.42 (0.0018)	0.39 (0.0015)	0.36 (0.0020)
3	0.52 (0.0091)	0.56 (0.0027)	0.50 (0.0021)	0.48 (0.0030)
4	0.61 (0.0110)	0.66 (0.0040)	0.59 (0.0028)	0.57 (0.0042)
5	0.69 (0.0129)	0.74 (0.0054)	0.66 (0.0036)	0.64 (0.0055)
6	0.74 (0.0148)	0.80 (0.0071)	0.72 (0.0044)	0.69 (0.0071)
7	0.79 (0.0171)	0.84 (0.0088)	0.76 (0.0053)	0.73 (0.0087)
8	0.82 (0.0190)	0.88 (0.0108)	0.79 (0.0062)	0.77 (0.0106)
9	0.85 (0.0214)	0.90 (0.0130)	0.82 (0.0074)	0.80 (0.0127)
10	0.88 (0.0228)	0.93 (0.0150)	0.85 (0.0086)	0.84 (0.0147)
20	0.98 (0.0279)	0.99 (0.0321)	0.96 (0.0221)	0.97 (0.0346)
32	1.00 (0.0274)	1.00 (0.0361)	1.00 (0.0280)	1.00 (0.0420)
33	1.00 (0.0274)			
34	1.00 (0.0274)			

SE: standard error.

2003 to 2005, about six new users per 100 000 inhabitants.

Table 2 shows the distributions of LP globally and by route of administration. Note that the three distributions by route of administration were truncated at 32 years of LP length to allow direct comparison (with stratified data there were null counts if larger LP periods were used). Overall, 50% of people delayed less than 3 years before entering treatment for the first time. Subjects already injecting at their first visit had a slightly higher probability of starting treatment earlier than the others (at 3 years of heroin use 56% of them had done so, whereas the corresponding figures for smoking and snorting were 50% and 48%, respectively).

DISCUSSION

We estimated that the incidence of problematic heroin use peaked in 1980 following a rapid increase from the early 1970s and declined rapidly until 2000, when a levelling-off was observed. This curve was similar by gender, although five times higher in men, and differed by route of administration; injecting heroin incidence peaked in 1980 then declined rapidly, whereas heroin smoking did not decline until 1990.

The method used develops Brookmeyer's approach [8], as suggested, by adopting log-linear modelling. As a consequence, a longer LP could be considered and more subjects contributed to the analysis. The approach used

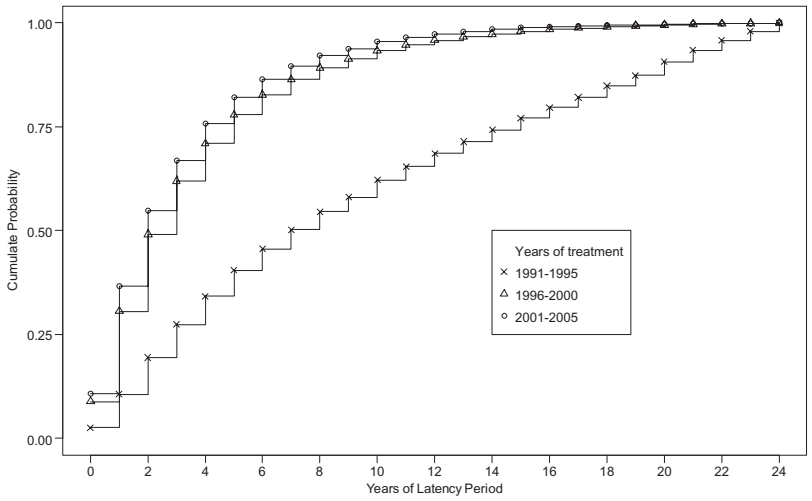

Figure 4 Latency period distributions of heroin use by three time-periods of treatment admission, Spain (latency period: years between first use and first treatment)

has permitted estimating incidence for practically the complete heroin epidemic in Spain, avoiding the limitation inherent in previous analyses that could only estimate incidence from the year the register started [7], and has provided an idea of the different relative importance of the two routes of administration during the epidemic. The large number of observations provided reasonable precision for the model estimates even after subdividing the database.

However, the treatment registry data employed can provide information only on heroin users who have been admitted into treatment in public or publicly funded centres during the observed interval. Heroin use incidence curves are thus limited to heroin users who might have been or will be admitted to heroin treatment in these centres: i.e. the incidence is conditional on ever starting a treatment. In this analysis we are not able to take into account those not observed because either their use was non-problematic, they were treated in private centres (of which there are very few in Spain) or they died or ceased use before ever requesting treatment. However, even with an underestimation of the magnitude of the problem, the incidence trend is an appropriate indicator to determine whether drug use is spreading (or diminishing), and if we assume that the proportion of non-observed users is constant from year to year the estimated trend will be similar to the real trend in incidence.

Our log-linear model approach implicitly entails independence; that is, the distribution of LP is the same for every year of onset. We assessed this by estimating LP distributions for three different treatment admission intervals: (A) 1991–1995, (B) 1996–2000 and (C) 2001–2005. The three distributions were truncated at 24 years of length in order to make them comparable. As observed in Fig. 4, people from (A) delayed longer before being admitted into treatment than people from (B) or (C). This could be explained because methadone maintenance programmes were incorporated gradually into treatment centres in Spain after early 1991, prompting a higher demand for treatment among both recent and veteran users, attracted by its effectiveness [18,19]. The LP distribution is thus affected by any change in the probability of users to seek treatment or in the 'attractiveness' of treatment centres to heroin users. The shapes of the estimated incidence trends for the periods B and C were similar to the global one, whereas that of period A was different, with a smoother rise until 1991 followed by a slow decline (data not shown). The assumption of independence is a limitation. However, for the present estimation we assumed that the global LP is an approximation to the real one, and the shape and trend of the estimated incidence can be considered as the best that can be obtained currently.

Certain fluctuations in the results may not be due only to the statistical methodology limitations. The validity of information collected about the two variables on which the method relies, heroin use onset and first admission to treatment, is difficult to assess. If the error in year of onset was random, as may be expected, it would not bias the incidence estimations. Conversely, errors in year of first treatment entail mistakenly considering the first treatment as a second or subsequent one, thus lengthening the LP calculated, and being a systematic error it would affect the overall trend. Further, currently the observed data and analyses do not take into account possible changes in route of administration between onset of use and first treatment, and so only provide incidence estimation by route of administration reported at first treatment.

From previous studies we have signs of a huge rise of new heroin users, mainly injectors, in Spain around 1980. For instance, an anthropological study performed in a Madrid neighbourhood stated that: in 1979, injecting heroin spread 'like fire in the grass' [20]. Also, the

peak of the HIV epidemic in Spain (where at that point injecting drugs was the predominant risk factor) was estimated to be between 1984 and 1987 [21], just 4–7 years after the estimated peak of heroin use incidence. This fact underscores the importance of the huge heroin epidemic in Spain and the importance of the decrease in heroin injection for the evolution of the human immunodeficiency virus (HIV), and probably hepatitis C virus, epidemics.

However, it is difficult to ascertain the reasons for such trends, and in fact problematic heroin incidence seems to have decreased even before there was any social or public concern about the existence of a 'heroin problem'. Socioeconomic conditions prevailing by the end of Franco's dictatorship and over the years which followed may have favoured its spread among young people [20]. Heroin market changes might help to explain why injecting was substituted by smoking [22,23] but are unlikely to have contributed to the large decrease of new users. The emergence of other substances considered less risky than heroin, such as cocaine or ecstasy, might have contributed to a shift of main drug of abuse, particularly in light of the severe consequences of the HIV epidemic in Spain [2]. Nevertheless, we consider it important to point out that the decrease of heroin incidence, particularly by injecting, has coexisted for several years with extensive development of harm reduction programmes, which can constitute evidence against the hypothesis that such programmes could contribute to spreading heroin use [24].

Using log-linear models we have been able to observe that the increase and later decrease in problematic heroin use incidence appeared much earlier than was thought from overall analysis of SDO indirect indicators [3], and that the decrease was related primarily to the fall of injecting. According to these indicators, a decrease of injecting as the main route of heroin administration occurred in some Regions in the late 1980s [12,13], but could not be observed in the context of a national incidence decrease until later on. Data from the present study allow us to see the actions taken to overcome the serious heroin epidemic in Spain in a new light: public health interventions clearly arrived late in various fields. In fact, it was not until 5 years after the heroin incidence peak (1980) that the National Plan on Drugs (an institution devoted mainly to 'solve' heroin problems) was created (1985); the information system with indirect indicators to monitor the problem was not available until 7 years had passed (1987); and 11 years had passed by the time relevant variables such as route of administration and information to distinguish first treatment demands from subsequent ones had been incorporated into the system (1991). Also, from the treatment viewpoint, methadone prescription, which began in the early 1980s at the individual physician's discretion, was restricted in 1985 to public treatment centres of recent establishment, and it was not until 1990 that methadone treatment was legislated with a wider scope [25]. It took several years to be implemented fully, needing an important change in physician practice from an abstinence-orientated philosophy to one of risk reduction. In some Regions it was not until 1995 that methadone maintenance programmes were accepted widely; this was 15 years after the epidemic peak, when probably a large proportion of those who had started use around 1980 had already died or were infected with, and possibly suffering the consequence of, HIV or hepatitis C virus [26].

Overall, our analysis provides further support for both the feasibility and relevance of estimating the incidence of problematic drug use with treatment data. Some methodological handicaps still exist which need to be solved, such as the problem of heterogeneity in the distribution of LP over the years.

Declarations of interest

None.

Acknowledgements

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8.2 Article 2: A multi-state model to estimate incidence of heroin use

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A multi-state model to estimate incidence of heroin use

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Abstract

Background: Existing incidence estimates of heroin use are usually based on one information source. This study aims to incorporate more sources to estimate heroin use incidence trends in Spain between 1971 and 2005.

Methods: A multi-state model was constructed, whereby the initial state "heroin consumer" is followed by transition to either "admitted to first treatment" or to "left heroin use" (i.e. permanent cessation or death). Heroin use incidence and probabilities of entering first treatment ever were estimated following a back-calculation approach.

Results: The highest heroin use incidence rates in Spain, around 1.5 per 1,000 inhabitants aged 10–44, occurred between 1985 and 1990; subdividing by route of administration reveals higher incidences of injection between 1980 and 1985 (a mean of 0.62 per 1.000) and a peak for non-injectors in 1990 (0.867 per 1,000).

Conclusions: A simple conceptual model for heroin users' trajectories related to treatment admission, provided a broader view of the historical trend of heroin use incidence in Spain.

Keywords: Back-calculation, Epidemiology, Heroin, Incidence, Multi-state model

Background

Recently, there has been increasing interest in ascertaining illegal drug use incidence for planning and evaluating prevention strategies [1]. In the case of heroin use, as survey data is not effective [2,3], incidence has been estimated from users eventually showing up mostly in treatment registers [1,4-9]. This incidence can be referred to as "problematic use incidence" and its trend could provide a satisfactory overview of problematic heroin use, assuming a constant proportion over total incidence.

The present study is an attempt to take the definition of problematic use incidence further by incorporating a proportion of individuals that used heroin who never show up in the main source under study (usually treatment). This proportion is based on other kinds of information, aggregated sources, estimates, or assumptions, such as mortality and cessation rates.

The idea is to study the unobserved entry (or immigration) of people to the state of "consumer", based on a later first entry to treatment. Since heroin users may exit the state of consuming heroin before entering treatment, whether due to death or permanent cessation of their consumption, a "left heroin use" state is added to the model. The situation is thus represented by a set of mutually related states, in a so-called multi-state model with immigration.

This approach has parallels in studies in the HIV field, where a multi-state model was presented describing progression of HIV disease from infection to AIDS in several stages [10,11] or Rossi's dynamic "mover-stayer" model as a theoretical approach applied to simulate a complete drug user "career" [12,13].

We shall use a back-calculation type approach to estimating the incidence. This is similar in spirit to de Angelis et al. [14]. However, following the presentation of Aalen et al. [10], we have found it useful to display the approach as a simple multi-state model.

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To our knowledge, previous approaches had to assume that treatment availability was stable over time [1,4-9]. As treatment data is usually only available for a limited period of time, a lag time distribution between heroin use onset and first treatment ever has been employed to avoid underestimating incidences. However, this assumption may be too strong if important changes in treatment availability had occurred. Therefore, the back-calculation approach used in this study avoids this assumption.

In Spain, heroin use generated important health problems in the eighties and early nineties [15], thereafter all indicators (mortality, treatment admissions, hospital emergencies, surveys, etc.) showed a decreasing trend until 2006 [16]. Efforts to calculate incidence of heroin use have been and still are considerable to understand the overall trend and assess its consequences [1]. To date only one previous study has estimated heroin use incidence in Spain. However, due to important changes of treatment availability, the reliability of the estimation was questionable [6].

The multi-state model approach may be successfully used to estimate heroin use incidence with the available Spanish heroin users' treatment data. We use the same treatment database as the previous study to assess differences in the incidence estimates depending on the approach used.

The objective of the present study was to estimate heroin use incidence in Spain through a multi-state model with immigration and assess differences with previous study's estimates.

Methods

Incidence estimation: the multi-state model with immigration

We will describe a heroin user's trajectory simply using the time of transition from state 1 (first heroin use) to one of two possible subsequent states: first treatment ever (state 2), or leaving heroin use before any treatment, either by permanent cessation or death (state 3) (Figure 1).

We shall now formulate our back-calculation type model. We let t be the calendar time and assume that the number of new heroin users per unit of time is Poisson distributed. The Poisson assumption is standard and well justified on statistical grounds [14]. Moreover, we let h_t denote the expected number of people entering state 1 (heroin use) at t. The number p_t denotes the probability that a given heroin user initiates their first treatment ever at time t, given that they were in state 1 at the previous time. We assume this probability independent of the era when their heroin use began. The number q_t denotes the probability of an individual leaving heroin use at time t, given that they were in state 1 at the previous time. The cause could be death or other permanent cessation of heroin use. We want to estimate the parameters h_t, the expected number of new heroin users at time t. The probability q_t is assumed known.

We now construct the likelihood function. This is a standard Poisson type likelihood, following the approaches in the basic back-calculation papers [14]. However, since our model is here adapted to the particular data we have, we briefly present the necessary formulas. Let N_{ij} be the observed number of individuals that start heroin use in year i and enter first treatment in year j. Let μ_{ij} be the expected value of N_{ij}. A short computation shows that:

$$\mu_{ij} = h_i \cdot \prod_{k=i}^{j-1} (1 - p_k - q_k) \cdot p_j \quad (1)$$

We see that μ_{ij} is the product of the expected number of new heroin users in year i (h_i), the probability that a given heroin user remains in state 1 from time i to time j-1 and the probability of a transition from state 1 to state 2 at time j. It also follows that each N_{ij} is Poisson distributed. This gives us the following simple expression for the likelihood:

$$L = \prod_{i,j} \mu_{ij}^{N_{ij}} \cdot \exp\left(-\mu_{ij}\right) \quad (2)$$

Maximizing this likelihood yields estimates for h_t and p_t.

Treatment data

The Spanish Drug Observatory maintains a drug information system. Its indicator "treatment" is based on data from all treatment starts in public and publicly funded

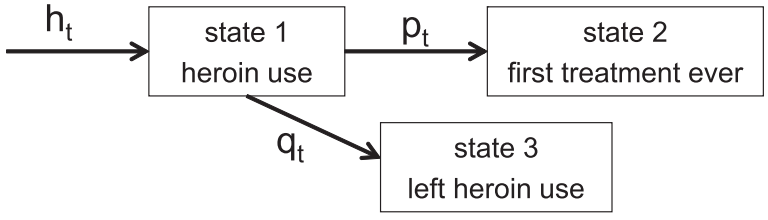

Figure 1 Multi-state model diagram. Parameter h_t denotes immigration of individuals starting heroin use, p_t transition rate entering treatment for the first time, and q_t transition rate leaving heroin use without entering treatment, at time t.

centres. The health coverage is universal and all kinds of treatment are considered. In the present study, we included 169,257 persons who entered first treatment for heroin use from 1991 to 2006 when aged 15 to 54 (mean 28 years), and who started their heroin use between 1971 and 2006 when aged 10 to 44 (mean 21 years). The database was split into two subsets: people who declared injection as the most frequent route for heroin use in the last 30 days before first treatment admission (29%) and people who declared using routes other than injection (68%). Route of administration was missing in 3% of persons.

Assumptions about parameters

As in all applications of back-calculation where a detailed history of individuals is not observed [14], we have to make some simplifying assumptions, presented below.

First treatment data for the period 1971–1990

In the estimation of p_t, first treatment data was available for t between 1991 and 2006, thus restricting estimates to this period. For the preceding part of the study period (t in 1971–1990), we made an educated guess of p_t based on general heroin use information in Spain. Based on the first appearances of admissions for heroin use in the emergency units in Spain in 1982 [17-19]; we assumed probabilities of entering treatment (p_t) as low as 0.01 between 1971 and 1981, as there were still no specific treatments available. Thereafter we assumed a linear increase to the value estimated for the parameter p_t in 1991.

Mortality for heroin users

Mortality rates for heroin users were only available from two local cohort studies covering the period 1985 to 1999 [20,21] in an area where injecting was the predominant route of administration [22]. As we did not have better approximation, yearly rates from these studies (minimum 1.4% in 1985, maximum 6.6% in 1995) were extrapolated to the whole country for the corresponding year. For the period 1971 to 1984 a smooth increasing trend from a mortality rate of 1% to 1.4% was applied. Mortality rates from 2000 to 2006 decreased from a rate of 1.5% in 1999, to 1% in 2006. In the analysis by route of administration the same mortality rate was used for injectors, but a constant mortality rate of 1% for non-injectors since they have lower risk [23].

Degenhardt et al. reported a pooled crude mortality rate of 2.09 per 100 person-years and that mortality risk was increased among out-of-treatment heroin users [24]. In a sensitivity analysis (see analysis section) we considered alternative mortality rates obtained by adding 0.01 to the yearly mortality rates in order to ensure a minimum rate of at least 2%. Note that, in the multi-state model we are imputing mortality rates before first treatment.

Cessation rates

Owing to the impossibility of obtaining permanent cessation rates, we looked for lasting cessation rates from long-term cohort studies. As such studies are not available in Spain, we considered yearly cessation rates from a thorough review which reported a range of 0.02-0.04 [25]. Our analyses considered these two extreme values.

Analysis

For all heroin users and for injectors and non-injectors separately, we applied the aforementioned multi-state model with the Spanish treatment data and the assumed leaving rates to estimate the heroin use incidence (h_t, t ranging from 1971 to 2006). As explained, the model also estimates the probability of entering first treatment (p_t, t in range 1991 to 2006). We considered the yearly cessation rate of 0.04 and the non-modified mortality rate derived from the local cohort studies. Note that the probability of leaving drug use without having ever been registered for first treatment (q_t) is the sum of the cessation and mortality rates for each year from 1971 to 2006.

In equation 1 when $i=j$, it means that users began treatment in the same year as they started heroin use. This gives on the average about half a year of observation, and so we must weight μ_{ij} by 0.5.

To assess the fit of the expected incidence values μ_{ij} with their observed values N_{ij}, we have drawn their curves stratified by year of heroin use onset (i).

As results can be dependent on assumptions, a sensitivity analysis was performed to evaluate the two chosen mortality and cessation rates obtaining four combinations of q_t, that are reflected in four curves of estimated incidence rates. These combinations were: firstly and as a matter of choice, the available mortality rates and a yearly cessation rate of 0.04; secondly, the same mortality rates and a yearly cessation rate of 0.02; thirdly, the same mortality rates modified by adding 0.01 to the rate for each year and a yearly cessation rate of 0.04; and finally, the modified mortality rates and a yearly cessation rate of 0.02.

Statistical uncertainty was estimated using a bootstrap technique with 500 re-samples, where each re-sample was made up of two parts: 1) the treatment database was re-sampled with replacement and, 2) both our "best guesses" for p_t in the period from 1971 to 1990, and the cessation rate for all years were sampled from gamma distributions. The shape and scale parameters were derived from the mean and standard deviation, taking

the mean as the "best-guess" value, and the standard deviation was established as 0.01.

The expected number of new heroin users per year was obtained, and converted into rates per 1,000 inhabitants, based on Spanish population yearly census data for people aged 10-44 [26].

Incidence estimates from the previous study were retrieved to compare with the present estimates. Both the period of years covered and the census figures were the same.

The software used for the statistical analysis was R version 2.13.0 [27]. The study was approved by the Ethics Committee of the Institution with number 2004/1828/I.

Results

Estimates of incidence and probability of entering treatment

Applying the multi-state model with immigration yielded estimated probabilities of entering treatment for the first time (p_t) which exhibited an overall increasing trend from 0.08 (95% CI 0.07-0.09) in 1991 to 0.29 (95% CI 0.23-0.49) in 2005. Incidence estimates of general heroin use and by route of administration with 95% confidence intervals are plotted in Figure 2. For general heroin use, the highest incidences were between 1985 and 1990 with rates around 1.5 new heroin users per 1,000 inhabitants aged 10–44, followed by a steep decline from 1991 to 1997, then a more gradual decrease from 1998 (0.24 per 1,000) to 2005 (0.05 per 1,000).

In the analysis by route of administration the probability of entering first treatment for heroin users declaring injection was higher than for non-injectors between 1991 and 2000 with a difference of around 0.03. However, after 2001 this difference increased progressively (Figure 3). Incidence rates for injectors were higher than for non-injectors until 1985 and lower thereafter (lower graph in Figure 2). For injectors the highest values were observed between 1980 and 1985 (a mean of 0.62 per 1,000) whereas for non-injectors the peak was in 1990 (0.86 per 1,000).

Comparing the curves of the expected incidence values μ_{ij} with their observed values N_{ij}, by year of heroin use onset (i), we assessed that the fit was good (Figure 4).

We could also check this good fit modifying the observed values as $N_{i,j-i}$ and the expected values as $\mu_{i,j-i}$, where j-i represents the lag time between drug use onset i from 1991

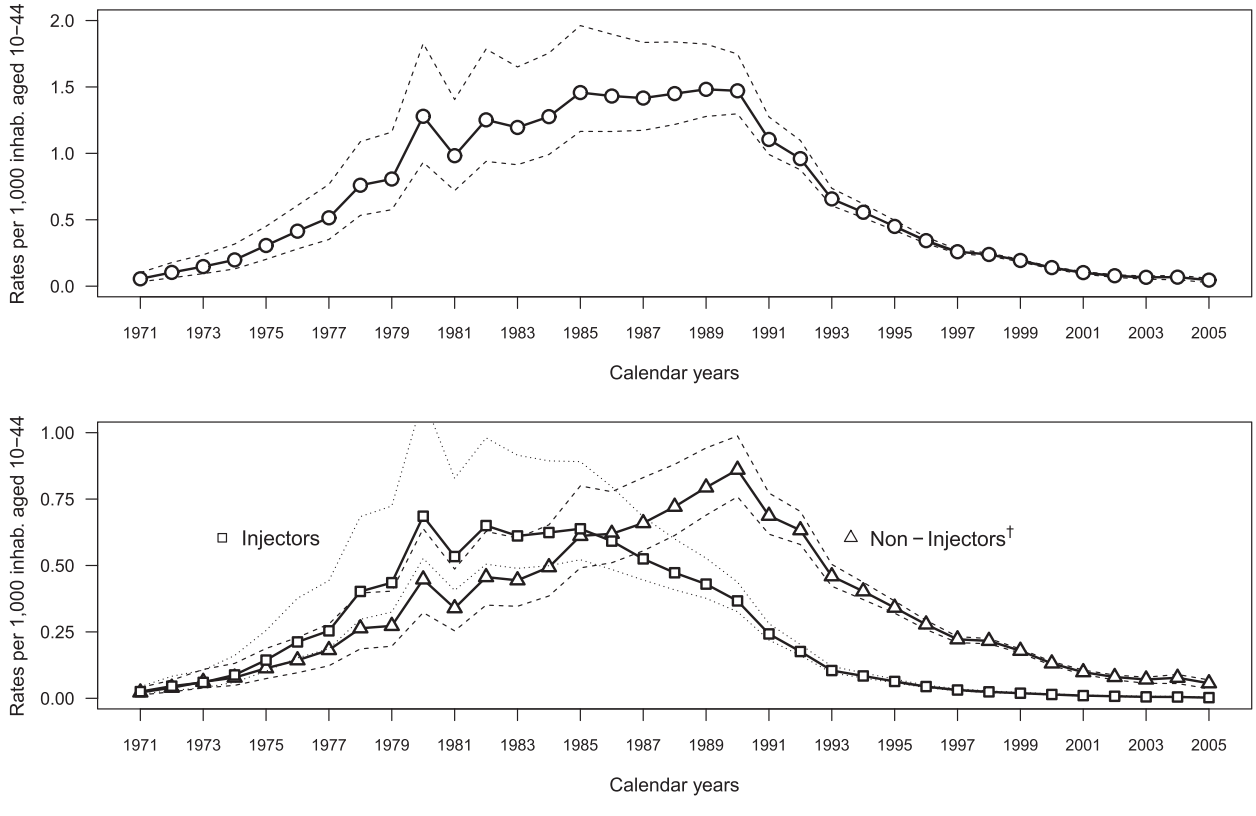

Figure 2 Estimated heroin use incidence rates*: global (upper graph) and by route of administration (lower graph).** * rates per 1,000 inhabitants aged 10–44, in Spain, with 95% confidence interval, ** the most frequent route of administration in the last 30 days before entering treatment.

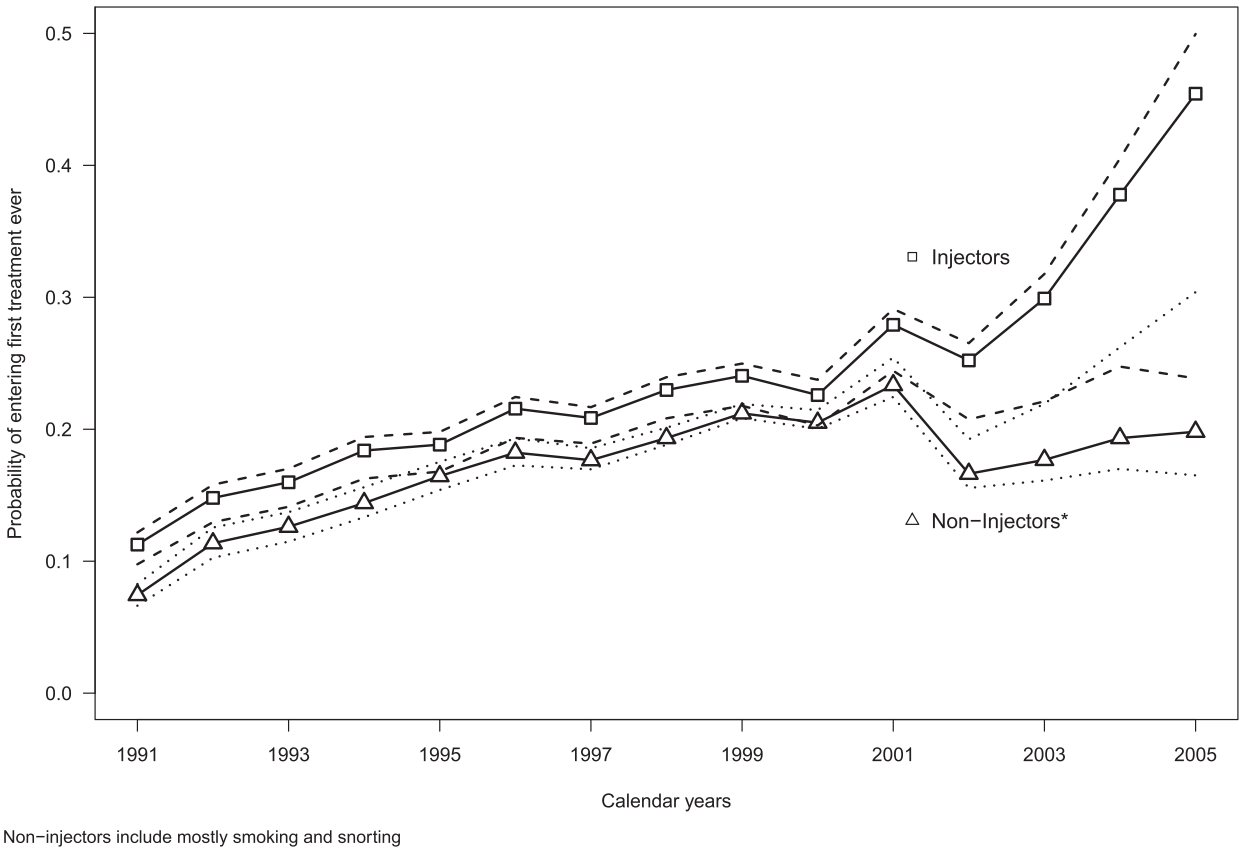

Figure 3 Estimated probabilities of entering first treatment ever (p_t) in Spain by route of administration, with 95% confidence interval.** ** The most frequent route of administration in the last 30 days before entering treatment.

to 2004 and first treatment ever *j*, conditional on treatment starting before 2006 (Figure 5).

Sensitivity analysis

Each combination of mortality and cessation rates produced large variations in the eighties when incidence was highest (Figure 6). Note that lower cessation and mortality rates yielded lower incidence rates, and vice versa.

Regarding probabilities of entering treatment for the first time, from 1991 to 2000 estimates only varied slightly, with a maximum difference of only 0.02 (data not shown). From 2001 differences increased progressively reaching a final value of 0.2 in 2005 between the lowest and highest combinations of cessation and mortality rates (probability of 0.22 versus 0.42).

Confidence intervals for the various estimates overlap, except for the combination yielding the lowest estimates (results not shown).

Comparison of incidence estimates

Incidence estimates from a previous study [6] are shown in Figure 6. These estimates had an earlier peak around 1980 and, although they were lower than present ones in the 90's, they overtook them in the last few years.

Discussion

We have established a conceptually simple multi-state model to obtain estimates for the incidence rates of heroin use and applied it over a long period in Spain. The highest incidences were observed from 1980 to 1985 corresponding to injectors and a peak in 1990 to non-injectors.

In comparison with previous studies, our estimates are wider in scope since by including mortality and other permanent cessation into the multi-state model it is possible to account for almost all problematic heroin users after drug use onset.

The conceptual model employed in this study focuses on the first phase of a heroin user's "career": from heroin use initiation to treatment. Other more complete models based on a theory of compartmental epidemic models over drug user "career" have also been described [12]. Adding more states into the model using the data available would, however, make estimating incidence too complex because heroin use cessation and relapse are frequent and difficult to follow up. Knowing first entry

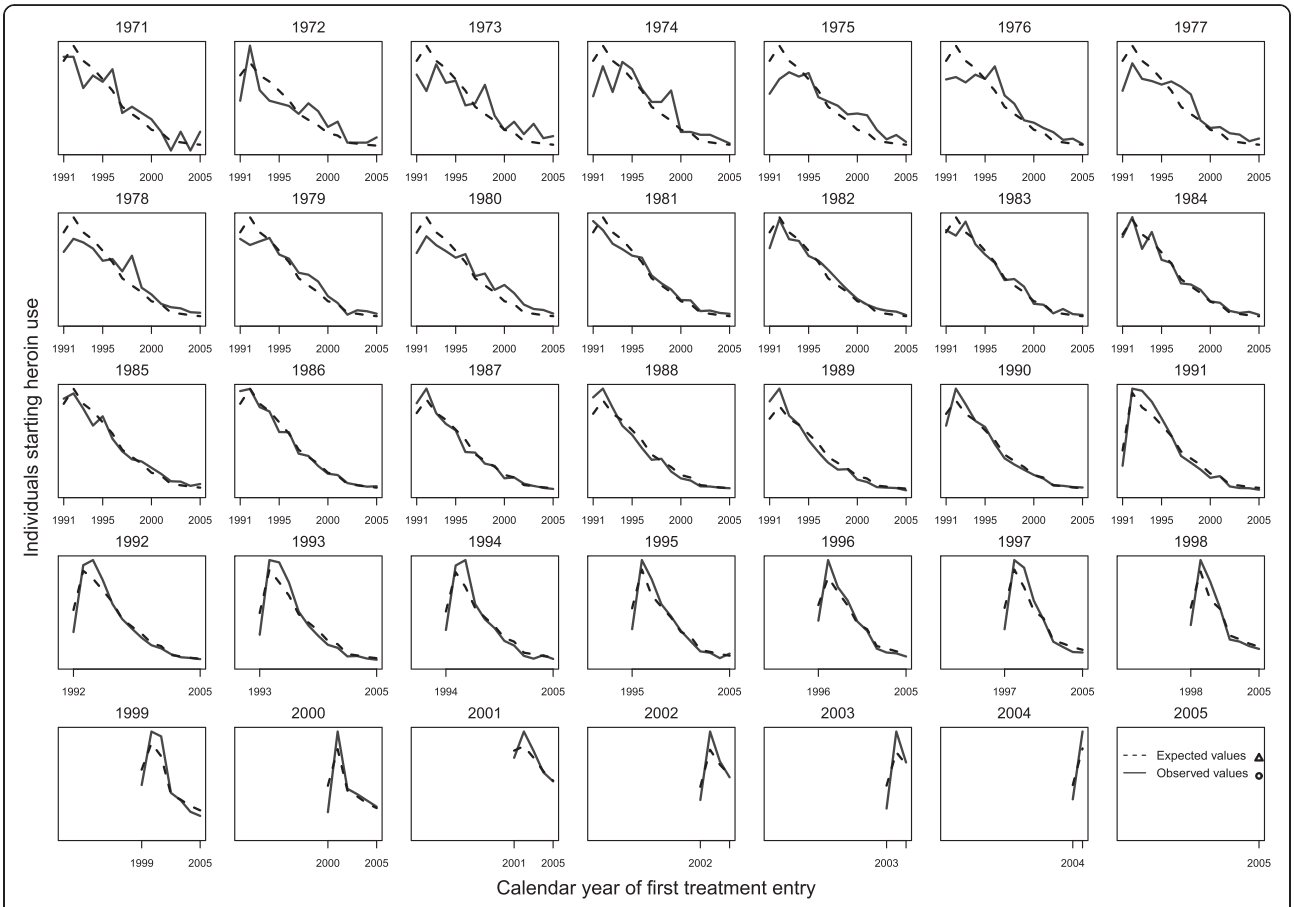

Figure 4 Observed and expected number of individuals by heroin onset cohort from 1971 to 2005, and entering first treatment ever from 1991 to 2005, in Spain.

to treatment and first use, we only need to account for quitting heroin use before first treatment through complete recovery (cessation) or death.

As a Spanish anthropologist described, in Spain heroin use had its first phase in the years 1977 and 1978, when the first users became visible, being endemic in the second phase between 1979 and 1982, and reaching its zenith between 1983 and 1986 leading to the institutionalization of the problem [18]. Therefore, trends in overall heroin use incidence obtained in the present study seem reasonable and consistent with previous knowledge about the Spanish heroin epidemic and the HIV-AIDS epidemic [15]. Specifically, the inflection point observed in 1985, when the incidence rate of injected heroin use fell below the rate for non-injection, is consistent with the trend of decreasing HIV incidence among injectors in Spain. However, we observe that estimates from the previous study had higher incidence figures earlier than the present ones (Figure 6). They reflect the fact that the availability of treatment was assumed stable throughout the entire period, leading to high estimates too soon.

We found a decreasing trend in the incidence estimates for the last years observed, which is probably related to the decreasing trend observed in all indicators towards the end of the period studied, as mentioned in the introduction. However, estimates for these last years from the previous study became stable overtaking the estimates from the present one (Figure 6). This is due to the two studies employing different approaches. Equation 1 in the present study was formulated assuming that p_t, the probability of entering first treatment, was independent of the era when a person's first heroin use began. Actually, this would be not entirely true if lag time between the drug use onset and first treatment followed a determined pattern, as previous studies assumed [1,6]. However, if we observe Figure 5, the lag time distribution for the observed values $N_{i,j\text{-}i}$ and for the expected values $\mu_{i,j\text{-}i}$ (j-i represents the lag time), for each year of heroin use onset from 1991 to 2004 all fitted well. So, to modify the equation 1 including the probability of entering first treatment conditional on the initiation of heroin use would be too complex and may not have great practical importance. Therefore, bias

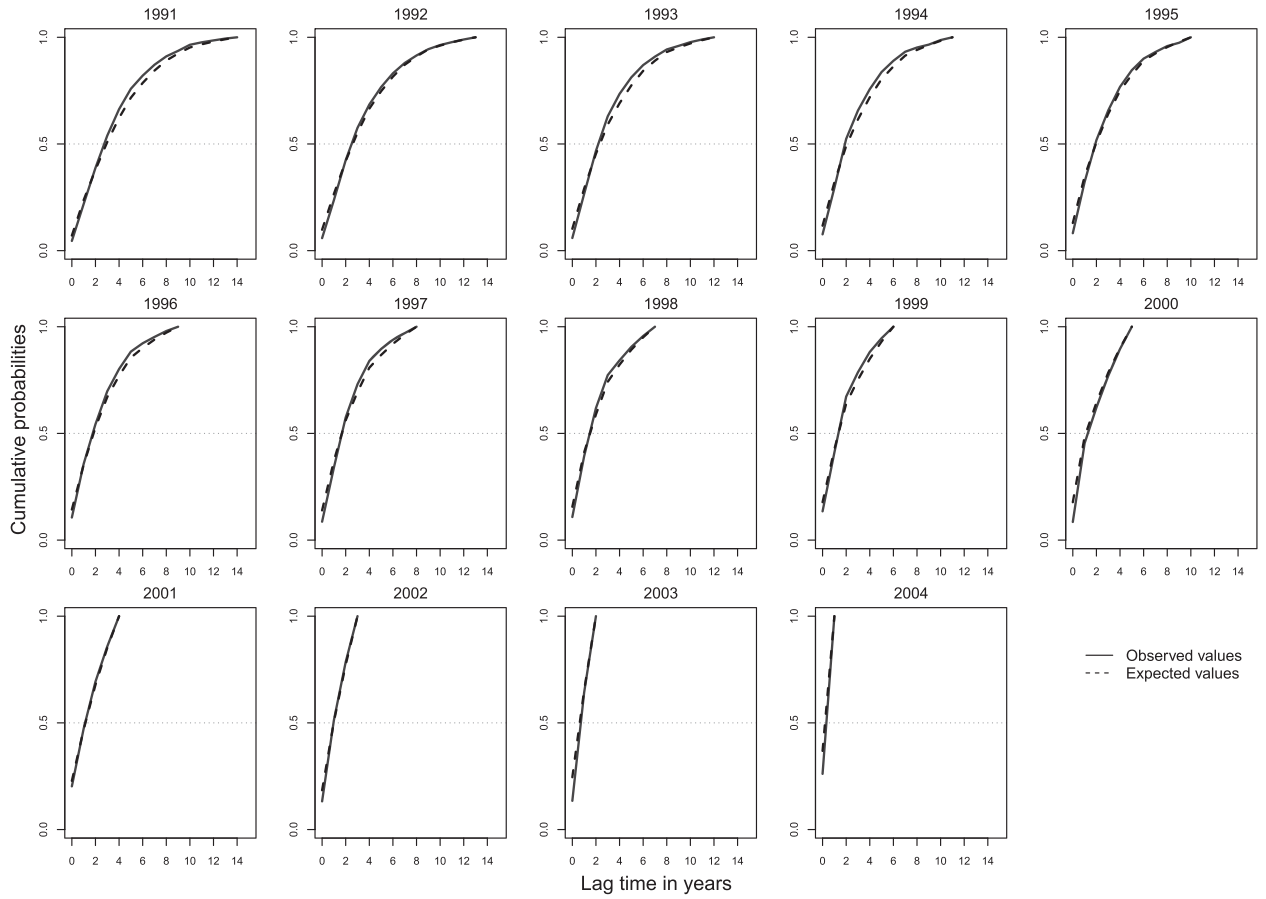

Figure 5 Observed and expected distributions of lag time between heroin use onset and first treatment ever conditional on treatment starting before 2006. Distributions are given by heroin onset cohort from 1991 to 2004, in Spain.

can be inherent in both the independence assumption and assuming a determined pattern of lag time, although the direction of such bias cannot be determined.

As observed by de Angelis [14], results are dependent on assumptions. However, the sensitivity analysis showed that the different incidence curves generated by varying the cessation and mortality rates had similar shapes (i.e. trends) although different levels, suggesting that the model's estimates were stable. Moreover, we observed that the confidence intervals of incidence figures estimated using non-modified mortality rates and a cessation rate of 0.04 completely contain those of the other three estimates. Thus the chosen incidence estimates do not differ significantly from the other three estimates, which resulted from varying the rates involved.

Concerning the assumptions made about the model parameters, such as 1) mortality rates, 2) permanent cessation, both before first treatment and 3) heroin users that started their first treatment before the observation period, we need to consider possible limitations:

1) Mortality rates were extrapolated by applying to the whole country figures from the North-East of Spain where heroin use injection was more frequent than in the rest of the country [22]. The extrapolation appears to be appropriate, since the period where the highest mortality rates are found for the two cohorts studied (1985 to 1999) coincides with the period when there were more HIV and drug injection related deaths in Spain [16]. However, if the extrapolation is not appropriate it would lead to over-estimation of the total incidence of heroin consumption for the whole country. Note that adding an additional 0.01 to the yearly mortality rates, i.e. to account for the risk of dying when out of treatment being greater, would lead to even greater overestimations of the incidence.

2) Using lasting cessation rates from long-term cohort studies would overestimate incidence as they include persons with long cessation periods who finally may relapse. On the other hand, the fact that experimental users were not included in studies estimating cessation rates would produce underestimates. Nevertheless, these experimenters are only of anecdotic value for policy interventions.

3) Although the exact dates and figures we have taken for first treatment probabilities prior to the observation

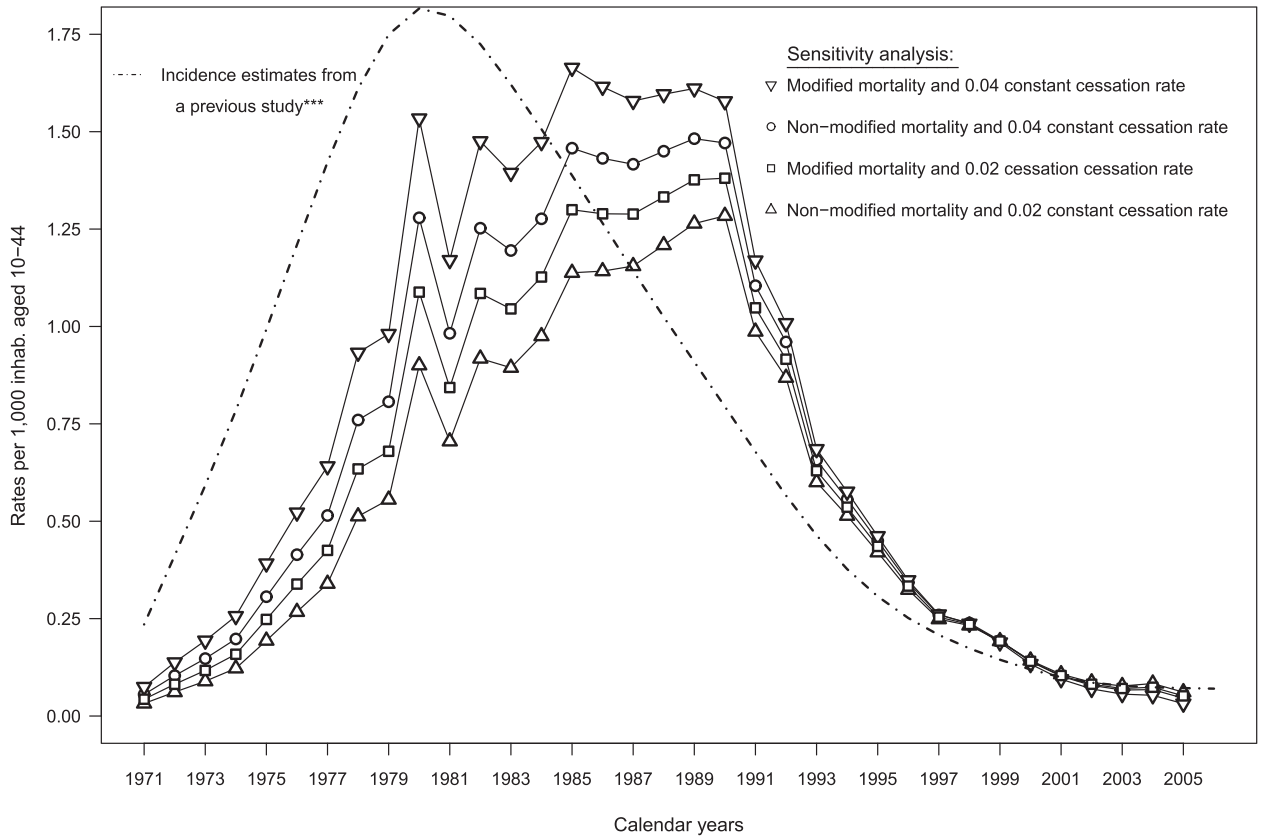

Figure 6 Sensitivity analysis* of heroin use incidence rates, and estimated incidence rates from a previous study***.** * combining two cessation rates and two mortality rates, ** per 1,000 inhabitants aged 10–44, in Spain, *** Sánchez-Niubò A et al. Problematic heroin use incidence trends in Spain. Addiction 2009; 104: 248–255.

period may not apply to the whole country, the values assumed seem plausible as we obtained an increasing sequence of probabilities from 1982 up to the first one estimated based on observed data in 1991, which happens to have a similar slope to that estimated in the observed period.

Besides model building, it is important to consider other limitations related to treatment data, both to its overall availability and to its accuracy. Treatment register data covers public and publicly funded centres, missing people using private treatment centres. This entails a small proportion especially once public substitution treatment centres were widely implemented all over the country following legislation in 1990 [28]. In relation to treatment variables used, we acknowledge the possibility of error in the reported year of heroin use onset, in which we cannot discern any systematic trend except perhaps a certain propensity to round to years ending in 0 or 5.

Incidence trends by route of administration do not necessarily reflect the route used at the time of onset, as the variable was collected referring to the 30 days prior to first treatment. However, in a previous study involving heroin users, both in and out of treatment, and a mean length of use of 10 years, more than 50% did not change their initial route of heroin administration [29]. Thus the study of incidence trends by route of administration in the period immediately previous to first treatment can provide an idea of the different patterns of heroin administration during the heroin epidemic in Spain [30]. The higher probability of entering treatment among individuals declaring injection in the previous month may possibly be related to a change to a more harmful route of administration.

Conclusions

With a simple conceptual model of heroin users' trajectories related to treatment demand, it has been possible to obtain approximations of heroin use incidence trends. Moreover, different assumptions made do not systematically skew the conclusions. However, enhancing accuracy of drug users' trajectories and an updating of new treatment admissions will further contribute to better incidence estimates.

Abbreviations
(HIV): Human immunodeficiency virus; (AIDS): Acquired immunodeficiency syndrome; (CI): Confidence interval.

Competing interests
The authors declare that they have no competing interest.

Authors' contribution
Albert Sánchez-Niubò participated in the study design, proceeded with data analysis and writing of the manuscript draft; Odd O. Aalen contributed to the design of the method and helped in the writing of the methodological part; Antònia Domingo-Salvany contributed to data acquisition, helped with the interpretation of the data and revised critically the draft for important intellectual content; Ellen J. Amundsen helped with the interpretation of the data and revised critically the manuscript for important intellectual content; Josep Fortiana helped in the analysis of the data and participated in the writing of the methodological part of the work; Kjetil Røysland designed the method implementation, supervised all the work and revised critically the manuscript. All authors approved the final version of the manuscript.

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8.3 Article 3: Incidence trends of cannabis and cocaine use from periodic Spanish GPS

Addiction
RESEARCH REPORT
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Incidence trends of cannabis and cocaine use from periodic Spanish general population surveys: effect of standardizing results by age structure

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ABSTRACT

Aims This study estimates life-time incidence trends of cannabis and cocaine use over 38 years from general population surveys of drug use (GPSDU) in Spain, taking into account changes of population age structure. **Design** Periodic cross-sectional studies. **Setting** Eight biennial GPSDU from 1995 to 2009 in Spain. **Participants** Interviewees aged 15–64 years who reported age of first ever cannabis and/or cocaine use between 10 and 64 years between 1971 and 2008. **Measurements** Estimates of raw and standardized incidences were calculated as a weighted mean of the incidences from all surveys. Standardization was conducted to take into account changes of population age structure. Incidence trends were extracted applying weighted cubic smoothing splines to incidence estimates. **Findings** For both substances, estimated raw incidence trends increased up until 2000 (rates of 11.5 ± 0.7 and 3.6 ± 0.5 per 1000, respectively, for cannabis and cocaine), and then decreased significantly (in 2008, 9.6 ± 1.2 and 2.7 ± 0.6, respectively). In contrast, standardized rates exhibit a steadily increasing trend up to 2000 (9.0 ± 0.6 and 2.8 ± 0.4), followed by a statistically non-significant increasing trend afterwards (in 2008, 9.5 ± 1.2 and 2.8 ± 0.6). The largest increases of incidence were observed in both male and female subjects aged 15–19 years. **Conclusions** Using data from Spanish general population surveys of drug use, an apparently decreasing trend of raw incidence rates in both cannabis and cocaine use from 2000 became non-decreasing trends when these rates were standardized. First experiences of cannabis and cocaine use in Spain occur mainly in younger ages (15–19 years).

Keywords: Cannabis, cocaine, epidemiology, incidence, standardization, survey.

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INTRODUCTION

The latest report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reveals that cannabis and cocaine are the most commonly used illegal drugs in the European Union (EU) [1]. In Spain, these two substances have life-time prevalences among the highest in the EU. Moreover, that for cannabis increased from 14.5% in 1995 to 32.1% in 2009, and that for cocaine from 3.4 to 10.2% over the same period [2].

In the field of health prevention there is considerable interest to complement data on substance use prevalence with data on incidence in order to evaluate and plan prevention policies adequately [3]. Information on drug use initiation can be extracted from two sources: indirect indicators such as admissions to drug treatment or health-care centres [3–5] and general population surveys on drug use (GPSDU) [6]. Indirect indicators reflect incidence related to problematic use (acute or chronic). In contrast, GPSDU may report a non-problematic use, especially when self-administrated questionnaires are used. However, population surveys have inherent biases that entail underestimation of incidence figures. Nevertheless, this method may be appropriate for observing yearly trends [7–10], comparing age-specific cumulative incidences by birth cohorts

[9,11–13] or determining hazard rates of age of drug use initiation [14,15].

Regarding estimation of yearly incidence trends, we found one study based on several surveys using what they called the retrospective method [7]. According to these authors, incidence estimates obtained retrospectively via periodically repeated samples from the same target population should permit more robust estimates of global incidence trends, while possibly reducing biases. They suggest that further research should be conducted taking the age structure of the population under study into account.

Several European countries have been carrying out GPSDU periodically, even though predated by and influenced by GPSDU in the United States [16]. However, very little information specifically concerning yearly incidence trends of cannabis or cocaine use from European GPSDU is available in the literature [17]. To our knowledge, two studies, from Greece and Amsterdam, applied the retrospective method to estimate incidence but only in the year prior to each survey [10,18]. Other studies, from England and Wales, estimated yearly incidence figures but from only one survey [8].

Concerning Spain, a recent study estimated age-specific cumulative incidences by birth cohort from GPSDU conducted biennially between 1995 and 2009 [13]. These cumulative incidences are informative about changes of age of onset between birth cohorts. Conversely, yearly incidence trends entail more direct information of overall use to inform health policies, so it is worth applying the retrospective method to these periodical GPSDU to estimate yearly incidence trends.

GPSDU permit obtaining information about first drug use, even when this occurred many years in the past. During that time, the population age structure may have undergone transformations, leading to changes in the age groups relevant for drug initiation. In Spain, from 1980 onwards, a negative growth has been observed in the population pyramid (see Appendix I) [19]. Therefore, we deemed it appropriate to control yearly incidence estimates for population age structure changes.

The purpose of this study is to estimate yearly incidence trends of cannabis and cocaine use from information gathered in the series of biennial GPSDU conducted in Spain during the period from 1995 to 2009, taking into account the age structure.

MATERIAL AND METHODS

Surveys on drug consumption

In Spain, the National Plan on Drugs (PNSD) has been conducting household surveys on drug consumption biennially since 1995, based on non-institutionalized individuals [2]. In total, eight surveys with similar sample designs are available (1995, 1997, 1999, 2001, 2003, 2005, 2007 and 2009). The 1995 edition of the survey did not employ a self-administered questionnaire, sampling was non-probabilistic and candidate subjects were aged 15 years or older. Since 1997, the survey questionnaires have been self-administered. Sampling designs have been variations on a basic theme of three-stage clustering without substitution: the first stage was either municipality (surveys 1997 and 1999) or census tract (2001 onwards); the second was either census tract (1997 and 1999) or household (2001 onwards); in the third stage an individual was chosen randomly within the household. From 1999 onwards, subjects aged 15–39 were oversampled, as they are more prone to use substances. Participation rates are not available for the surveys from 1995 to 2001, while from 2003 to 2009 rates were slightly greater than 50%. Knowing these response rates, samples were oversized accordingly to achieve the desired effective numbers. The final weighted samples from all surveys had age and sex distributions similar to their corresponding general population structure (see Appendix I).

The information about year of first use of cannabis and cocaine was reported in terms of the age of first consumption. Furthermore, for each survey, each individual was weighted according to sampling design.

To homogenize the samples of all surveys, we applied several restrictions: age at time of survey between 15 and 64 years; age at first consumption between 10 and 64 years; and year of first consumption no earlier than 1971; individuals who reported first consumption in the survey year were not accounted for because interviews were conducted throughout that year. The final sample sizes for each survey from 1995 to 2009 comprised 8888, 12 304, 12 234, 14 113, 12 033, 27 934, 23 715 and 20 109 individuals. The proportions of people who declared having ever used cannabis or cocaine, but for whom age of first use was missing or less than 10 years old, were approximately 3 and 6% for cannabis and cocaine, respectively, in 1995, and less than 1% for the rest of the surveys.

Cross-tables: calendar year by age of first drug use

We considered a cross-table s for each survey whose entries, defined by $n_{th}^{(s)}$, were the number of individuals within the total population whose first drug use occurred at age h in year t. Weights for each individual of the sample within the total population were applied. Additional details of the structure of these cross-tables are given in Appendix II.

Raw rates of drug use incidence by survey

In each cross-table, the marginal values for each year t give the weighted frequency of individuals reporting first drug use in that calendar year. To obtain the corresponding rates we need c_t, the Spanish census population for each calendar year t, for the same age range as our first use values [19]. We denoted these rates by $r_t^{(s)}$ and calculated them as follows:

$$r_t^{(s)} = \sum_h n_{th}^{(s)} / c_t$$

Standardized rates of drug use incidence by survey

As the distribution of ages of the Spanish population changed over the years studied, as also in the samples from each survey, we applied the method of direct standardization to obtain comparable rates, considering the population obtained by the latest census (2008) as the standard [20]. Yearly age-specific rates, $r_{th}^{(s)}$, were calculated as follows:

$$r_{th}^{(s)} = n_{th}^{(s)} / c_{th},$$

where c_{th} is the Spanish census figure for calendar year t and age h.

These rates were then standardized using the age distribution from the 2008 census, as the reference for all calendar years. Therefore, for each survey s, standardized rates of drug use incidence by each year t were calculated as follows:

$$z_t^{(s)} = \sum_h r_{th}^{(s)} \cdot c_{2008,h} / c_{2008}$$

Estimation of drug use incidence

Following Gfroerer & Brodsky [7], an estimate of incidence for each calendar year was obtained by combining contributions from the available surveys. The composite estimate x_t for year t is the weighted average:

$$x_t = \sum_{\forall s>t} q_t^{(s)} \cdot x_t^{(s)},$$

where $x_t^{(s)}$ is either the raw ($r_t^{(s)}$) or the standardized ($z_t^{(s)}$) rate of incidence for year t and survey s, and $q_t^{(s)}$ is the weight:

$$q_t^{(s)} = \left(Var\left(x_t^{(s)}\right)\right)^{-1} \Big/ \sum_{\forall s>t} \left(Var\left(x_t^{(s)}\right)\right)^{-1}$$

Variances of each $x_t^{(s)}$ were estimated using a bootstrap technique with 1000 resamples with replacement for every survey s.

We employed weighted cubic smoothing splines in order to extract smoothed fitted trends and their 95% confidence intervals from the incidence estimates over time. Conversely, we employed weighted linear regressions to check whether slopes were significant in a specific subset of years. The weights used in both analyses were the same as used to calculate the composite estimates.

The entire above procedure was also employed to estimate standardized incidence rates per 1000 inhabitants and their trends by gender and age groups of first use (10–14, 15–19, 20–34 and 35–64 years) for both substances. Finally, we estimated standardized incidence rates per 1000 inhabitants for both substances for three groups of surveys (1995–99, 2001–05 and 2007–09), but restricting the age of first use to 15–19 years. We employed Student's t-tests to evaluate differences in the incidence estimates between the three groups of surveys.

The software used for all computations was R version 2.15 [21].

RESULTS

Following the retrospective method, we obtained composite estimates, their trends and 95% confidence intervals of raw and standardized rates of cannabis and cocaine incidence for ages of onset from 10 to 64 years (Fig. 1). For cannabis, both incidence curves, raw and standardized, exhibit increasing trends in all years until 2000 (raw rate of 11.5 ± 0.7 per 1000 and standardized rate of 9.0 ± 0.6), slopes in the 1970s and 1990s being particularly steep. Conversely, from 2000, the raw incidence decreased significantly (9.6 ± 1.2 per 1000 in 2008), whereas the standardized incidence continued to increase, although not significantly (9.5 ± 1.2 per 1000 in 2008). For cocaine, both curves also showed increasing trends up to approximately 1999 (raw rate of 3.6 ± 0.5 per 1000 and standardized rate of 2.8 ± 0.4), after which raw incidence decreased significantly (2.7 ± 0.6 per 1000 in 2008), whereas the standardized curve remained stable (2.8 ± 0.6 per 1000 in 2008). These differences of slope between raw and standardized incidence trends reflect differences in the population age structure over the period studied.

Figure 2 presents the estimated trends of standardized rates of cannabis and cocaine use incidence, with 95% confidence intervals, by gender and age groups. The group aged 15–19 years had the highest standardized rates for both substances and both genders; males had higher rates than females (for cannabis, in 2008, 117.5 ± 21.5 per 1000 in males and 83.8 ± 18.6 per 1000 in females). In that age group, rates for cannabis were increasing steadily in both genders but non-significantly after 2000, whereas rates for cocaine had the steepest upward slope at the end of the 1990s, with a stable trend afterwards (in 2008, 34.1 ± 11.1 per 1000 in males and 12.2 ± 6.8 per 1000 in females). The age

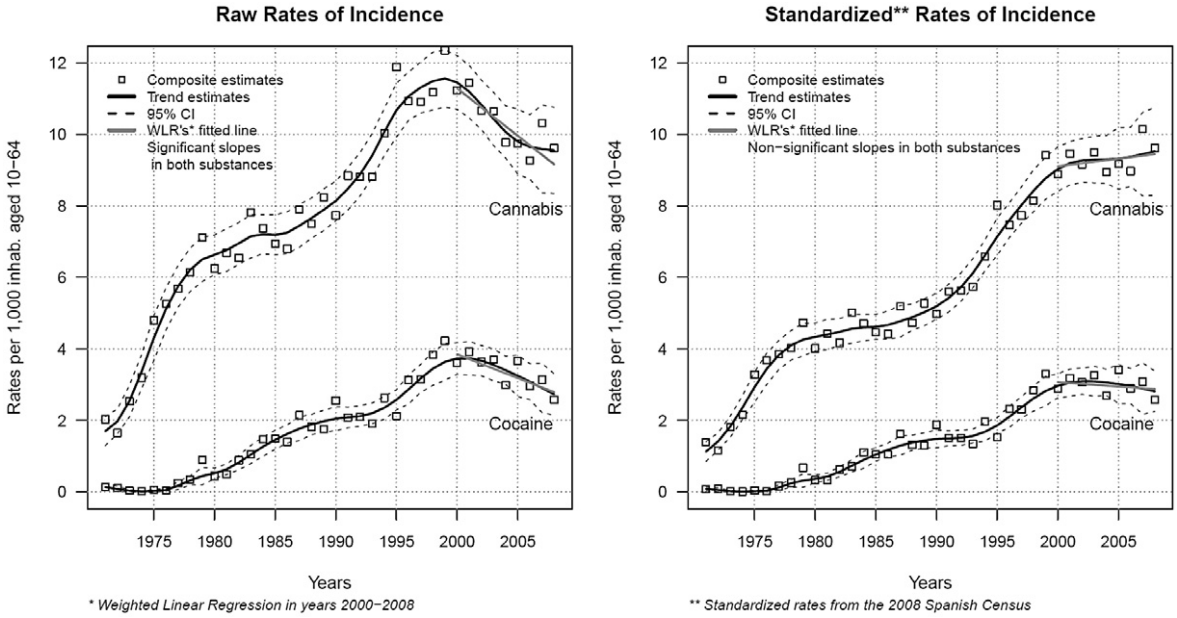

Figure 1 Composite estimates, their trends and 95% confidence intervals of raw and standardized rates per 1000 inhabitants aged 10–64 years of cannabis and cocaine use incidence from biennial surveys between 1995 and 2009 in Spain

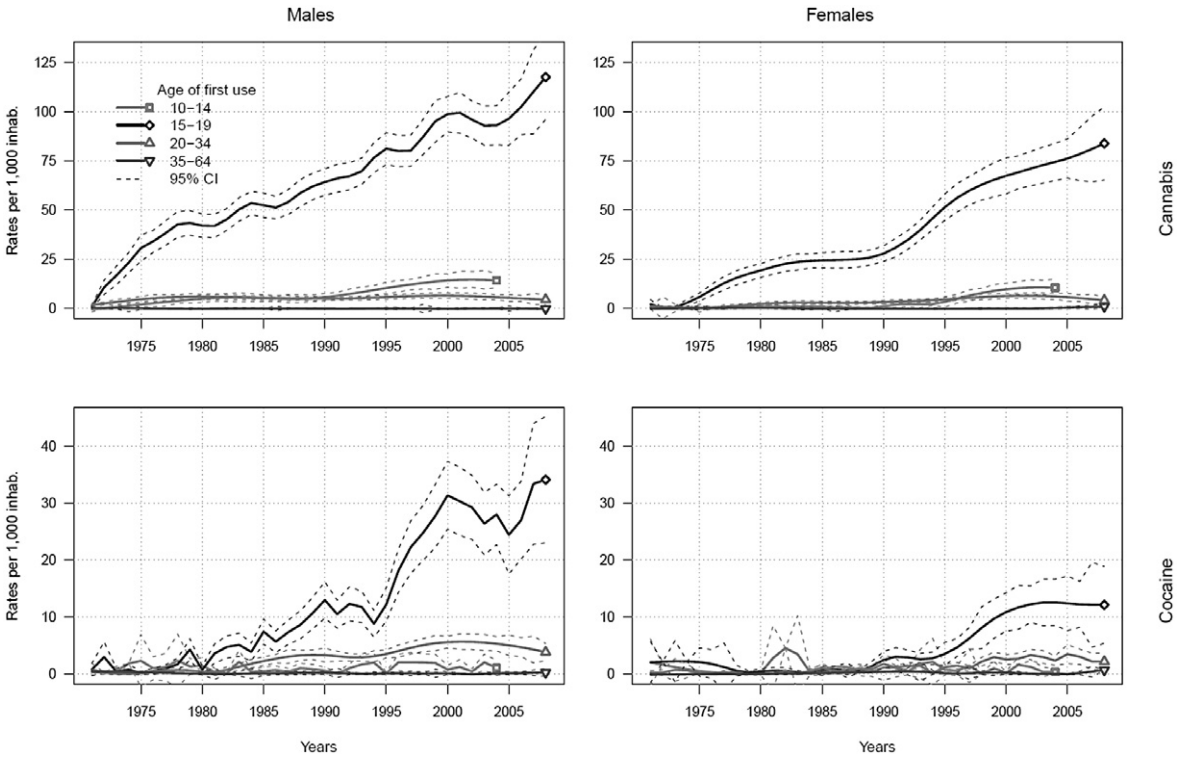

Figure 2 Trend estimates and their 95% confidence intervals of standardized rates per 1000 inhabitants by gender and age group (10–14, 15–19, 20–34 and 35–64 years) of cannabis and cocaine use incidence from biennial surveys between 1995 and 2009 in Spain

groups ranking second in terms of incidence rates were, for cannabis, those aged 10–14; for cocaine, those aged 20–34. Note that for the group aged 10–14, rates after 2004 were not calculated because incidence was truncated (see Appendix II).

Table 1 shows the comparison of the estimated trends of standardized incidence rates in both substances for age at first use lying in the range 15–19 years, in three subgroups of surveys, 1995–99 (S1), 2001–05 (S2) and 2007–09 (S3). For cannabis, incidence rates from the S2

Table 1 Estimates of standardized incidence trends of cannabis and cocaine use per 1000 inhabitants aged 15–19 years by three groups of surveys: 1995–99 (S1), 2001–05 (S2) and 2007–09 (S3), in Spain.

Cannabis										*Cocaine*									
							Student's t-statistic										*Student's t-statistic*		
	S1	*SD*	*S2*	*SD*	*S3*	*SD*	*S1 versus S2*	*S1 versus S3*	*S2 versus S3*		*S1*	*SD*	*S2*	*SD*	*S3*	*SD*	*S1 versus S2*	*S1 versus S3*	*S2 versus S3*
1971	4.9	3.03	7.2	2.06	6.5	1.57	−0.62	−0.45	0.28	1971	2.44	3.41	0.83	0.69	1.35	0.70	0.46	0.31	−0.53
1972	7.7	1.76	7.6	1.43	8.5	1.69	0.04	−0.36	−0.44	1972	1.60	1.73	0.49	0.52	1.12	0.51	0.61	0.27	−0.86
1973	10.5	1.98	11.1	2.04	11.1	2.04	−0.22	−0.21	0.01	1973	0.81	0.75	0.21	0.16	0.91	0.36	0.78	−0.12	−1.79
1974	13.3	1.79	15.7	1.87	15.6	1.48	−0.94	−1.00	0.04	1974	0.37	0.33	0.18	1.50	0.82	0.31	0.12	−1.00	−0.42
1975	16.2	3.41	21.4	1.98	20.8	2.39	−1.33	−1.11	0.19	1975	0.43	0.89	0.08	0.08	0.93	0.44	0.39	−0.50	−1.89
1976	18.9	2.21	26.3	2.01	25.1	2.27	−2.45*	−1.93	0.40	1976	0.24	0.17	0.39	0.20	1.10	0.44	−0.57	−1.84	−1.48
1977	21.6	2.05	30.0	2.35	28.4	2.39	−2.70*	−2.15*	0.49	1977	0.41	0.25	0.98	0.66	1.32	0.33	−0.82	−2.17*	−0.45
1978	24.0	4.71	32.2	2.52	30.6	2.35	−1.54	−1.26	0.47	1978	0.89	0.32	1.15	0.46	1.64	0.38	−0.46	−1.52	−0.83
1979	26.2	2.76	32.9	1.94	32.2	2.26	−1.99	−1.70	0.22	1979	1.76	0.68	0.91	1.04	2.17	0.42	0.68	−0.51	−1.12
1980	28.0	3.00	33.7	2.68	33.5	2.13	−1.40	−1.48	0.05	1980	2.02	0.49	0.71	0.29	2.82	0.46	2.30*	−1.18	−3.86*
1981	29.7	2.24	36.5	2.42	35.3	1.91	−2.07*	−1.91	0.39	1981	2.12	0.44	1.63	0.93	3.54	0.48	0.48	−2.18*	−1.84
1982	31.3	2.06	40.1	2.08	37.4	2.15	−3.04*	−2.06*	0.93	1982	2.29	0.47	2.66	0.59	4.29	0.59	−0.48	−2.63*	−1.94
1983	32.7	1.97	43.7	2.54	38.9	1.92	−3.42*	−2.23*	1.52	1983	2.39	0.69	3.35	0.77	5.03	0.61	−0.93	−2.88*	−1.71
1984	34.2	2.06	44.8	2.78	39.8	1.83	−3.07*	−2.04*	1.50	1984	2.62	0.65	3.59	0.52	5.79	0.74	−1.16	−3.22*	−2.43*
1985	35.7	2.29	43.3	2.11	40.8	1.80	−2.44*	−1.76	0.89	1985	3.84	0.87	3.52	0.59	6.50	0.74	0.31	−2.33*	−3.16*
1986	37.2	2.24	42.0	3.01	42.1	1.83	−1.28*	−1.71	−0.05	1986	4.90	0.81	3.48	0.76	7.14	0.60	1.29	−2.22*	−3.79*
1987	38.8	3.30	42.9	2.02	43.9	1.78	−1.06	−1.35	−0.35	1987	5.50	0.93	4.38	0.64	7.76	0.59	0.99	−2.05*	−3.86*
1988	40.6	2.72	44.5	2.30	45.6	1.89	−1.08	−1.48	−0.36	1988	5.68	0.96	5.99	0.67	8.41	0.61	−0.27	−2.40*	−2.65*
1989	42.6	2.58	45.7	2.39	47.1	2.04	−0.88	−1.35	−0.43	1989	5.75	0.89	7.85	1.07	9.14	0.65	−1.51	−3.09*	−1.03
1990	44.8	2.74	47.8	2.28	48.5	2.52	−0.83	−1.00	−0.22	1990	6.08	0.90	9.41	1.30	9.98	0.80	−2.10*	−3.23*	−0.37
1991	47.1	3.23	51.0	2.30	50.8	2.40	−0.98	−0.94	0.04	1991	6.12	0.82	10.39	1.33	10.93	0.81	−2.74*	−4.19*	−0.35
1992	49.5	2.72	54.9	2.29	54.2	2.36	−1.53	−1.30	0.23	1992	5.61	0.87	10.72	1.21	12.05	0.79	−3.43*	−5.49*	−0.92
1993	52.0	4.40	60.0	2.44	58.6	2.01	−1.60	−1.36	0.46	1993	4.73	0.86	10.56	0.87	13.33	0.82	−4.76*	−7.21*	−2.31*
1994	54.5	4.40	66.0	2.75	63.2	2.55	−2.21*	−1.71	0.74	1994	4.47	1.19	10.38	0.90	14.70	0.93	−3.95*	−6.78*	−3.33*
1995	57.1	9.31	71.8	2.89	67.0	3.76	−1.51	−0.98	1.03	1995	6.03	0.96	10.66	1.15	16.14	0.88	−3.08*	−7.76*	−3.78*
1996	59.6	4.07	76.9	3.13	69.2	2.32	−3.37*	−2.04*	1.98	1996	9.07	1.74	11.83	1.48	17.54	1.24	−1.21	−3.96*	−2.96*
1997	62.1	6.84	80.8	3.28	71.4	2.96	−2.47*	−1.24	2.14	1997	12.66	3.26	14.05	1.08	18.77	1.37	−0.41	−1.73	−2.70*
1998	64.6	5.95	83.5	3.26	74.4	2.40	−2.79*	−1.53	2.26	1998	16.51	5.23	16.56	1.58	19.78	1.38	−0.01	−0.61	−1.54
1999			85.4	3.19	77.7	3.30			1.69	1999			18.71	2.29	20.55	1.32			−0.70
2000			86.7	3.13	79.9	2.85			1.62	2000			20.10	2.36	21.10	1.34			−0.37
2001			87.8	3.14	81.1	2.43			1.68	2001			20.75	1.94	21.42	1.31			−0.29
2002			88.5	3.26	81.5	2.17			1.79	2002			20.97	1.70	21.55	1.04			−0.29
2003			89.3	3.98	81.9	2.43			1.60	2003			21.12	1.72	21.54	0.87			−0.22
2004			89.9	5.50	83.1	2.91			1.08	2004			21.17	2.00	21.50	0.98			−0.15
2005			85.9	3.02						2005					21.50	1.21			
2006			90.5	2.61						2006					21.59	1.27			
2007			96.2	3.91						2007					21.75	1.46			
2008			102.3	5.57						2008					21.95	1.86			

*P-value < 0.05. SD = standard deviation.

surveys were higher, even though only significantly so compared to those from the S1 group. For cocaine, incidence rates from S3 were significantly higher than the other two groups of surveys. Note also that in the 1990s, cocaine incidence rates from S1 were significantly lower than the other two groups of surveys.

DISCUSSION

The present study shows that an apparently decreasing trend of raw incidence rates both in cannabis and cocaine use in recent years became non-decreasing trends when these rates were standardized. Moreover, first experiences of drug use occurred mainly in younger ages (15–19 years).

Standardization has been used in prevalence studies [22]; however, to our knowledge no previous study has focused on standardized yearly incidence trends with which to compare our results. When comparing Spanish incidence trends with other European studies from Greece, Amsterdam, England and Wales, we observed that in Spain cannabis use incidence increased more steeply [8,10,18]. Conversely, our trend for cocaine was similar to that for Amsterdam, with slightly lower rates [18]. In the United States incidence began to rise approximately 10 years earlier [9]. Moreover, incidence trends there showed a smooth decrease from the 1990s onwards, in contrast to the apparently continuous increase of cannabis use incidence and stable cocaine use incidence observed in Spain from 2000 onwards. A study of treatment admissions to detoxification centres in Barcelona City produced estimates of cocaine use incidence, with an increasing trend similar to the present study, although with rates of approximately half [4]. In general, all studies agree that younger ages have the highest incidences, actual ages for cannabis being younger than for cocaine. The age structure of different countries should be taken into account to tune the observed results more finely.

We must take into account that retrospective estimates from cross-sectional studies may have important biases, resulting in underestimates. One bias is due to differential mortality, as people who have started drug use are more likely to have died before the survey year. However, there is no evidence that mortality from cannabis and cocaine use is higher than for the general population [23,24]. A bias due to fear of disclosure of their illicit drug use would also contribute to underestimation. However, from 1997 onwards the questionnaire about drug use was self-administered, the aim being to minimize this bias. Note that we assume that the fear of disclosure did not change for either substance over the various surveys. Another bias may be due to population coverage, as some homeless and institutionalized people (particularly in prisons) could have a higher risk of having used substances. Recall bias is somewhat more complicated. Retrospective reporting of events in the past entails inherent memory bias, involving mainly the misperception that past events occurred more recently than they actually did, called 'forward telescoping' [25]. A systematic effect of forward telescoping would underestimate an increasing incidence trend and overestimate a decreasing trend. Therefore, fluctuations in the real trend could interact with an estimated trend. As in the present study, estimated trends are mainly increases; assuming forward telescoping, incidence rates would also be underestimated. Note that in younger ages, for recent surveys, incidence estimates should not have this effect, and those are the more interesting years for health policy. Despite efforts to enlarge the initial samples, poor response rates would contribute even more to underestimating incidences. All these previous biases, found commonly in GPSDU, lead in general to figures that underestimate incidence.

Taking into account eight surveys, the coverage is wider but not total: some individuals who had initiated drug use were not interviewed because they did not fall into the age range required by the survey. Conversely, we have seen that the group aged 15–19 had the highest incidences, and this age range is covered completely by all eight surveys (see Appendix II). Therefore, global incidence figures cannot be greatly underestimated. Because, for cannabis, the group aged 10–14 years had the second highest incidence rates (although still very low), incidence estimates for all ages in the most recent years could be underestimated slightly.

Although the 1995 survey used a slightly different design from the rest, it was providing more age coverage for the composite estimate, and after assessing that its influence on estimates was slight we decided to include it.

In the United States, reports from the National Household Survey on Drug Abuse noted that they do not present findings for incidence of consumption due to lack of validity of the magnitude of the estimates, although this is not the case for trends [26]. In our case, Table 1 shows that the direction of trends for the three groups of surveys are very similar. In general, we found that more recent surveys had significantly higher incidence rates, perhaps suggesting that changes in societal perceptions of cannabis and cocaine use may reduce under-reporting over time.

We would like to point out that we are providing data for first occurrences of cannabis and cocaine use, and as such they would involve mainly experimental users. Drug use initiation does not imply a subsequent habitual use, and differences in this evolution have been observed by gender and country [1]. Nevertheless, first use is important as it provides the path to problematic use, especially

at the observed young ages. Following Rose's prevention theory [27], attention also needs to be directed to experimental use.

Raw incidence data may be useful for evaluating the overall level of services needed, but standardized incidences provide a closer approximation to the real trend in the relevant population, important for prevention and to evaluate interventions. Thus, in populations where the age structure suffers important changes over time, calculated trends will vary and hence age standardization is needed to make incidences comparable between different years.

As incidence rates for both substances were highest among the youngest age groups throughout the whole period, efforts in prevention should start well before 15 years of age. Both genders need to be considered because, although lagging behind to some extent, cannabis use incidence in females aged 15–19 had a steeper increase and in recent years approached male incidence rates. These results correspond with findings at European level where the rate of experimental use in men was double that in women, although a decrease in this difference was observed recently [1]. This suggests the need to consider gender when investigating both patterns of use and their consequences [13,28,29].

Yearly incidence figures composed from periodic surveys provide a more robust estimation of incidence trends due to increased precision and wider age coverage. Furthermore, they allow information bias assessment (Table 1). As more and more countries are conducting periodic GPSDU the availability of longer series will make calculation of composite incidence more feasible, implying that interest in this indicator is likely to increase. We emphasize that in such cases standardization should be applied.

The present study shows that the incidence trends of cannabis and cocaine use over a period of almost 40 years vary, depending upon whether or not the population age structure is taken into account. Standardized incidences have highlighted the presence of a non-decreasing trend, due mainly to the fact that first experiences of cannabis and cocaine use were still frequent among younger individuals. Prevention strategies should be aware of these findings.

Declarations of interest

None.

Acknowledgements

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APPENDIX I

Figure A1 shows the population age structures graphically by sex as population pyramids for 1995 and 2009 in Spain. These pyramids also contain two age structures, extracted from the general population surveys of drug

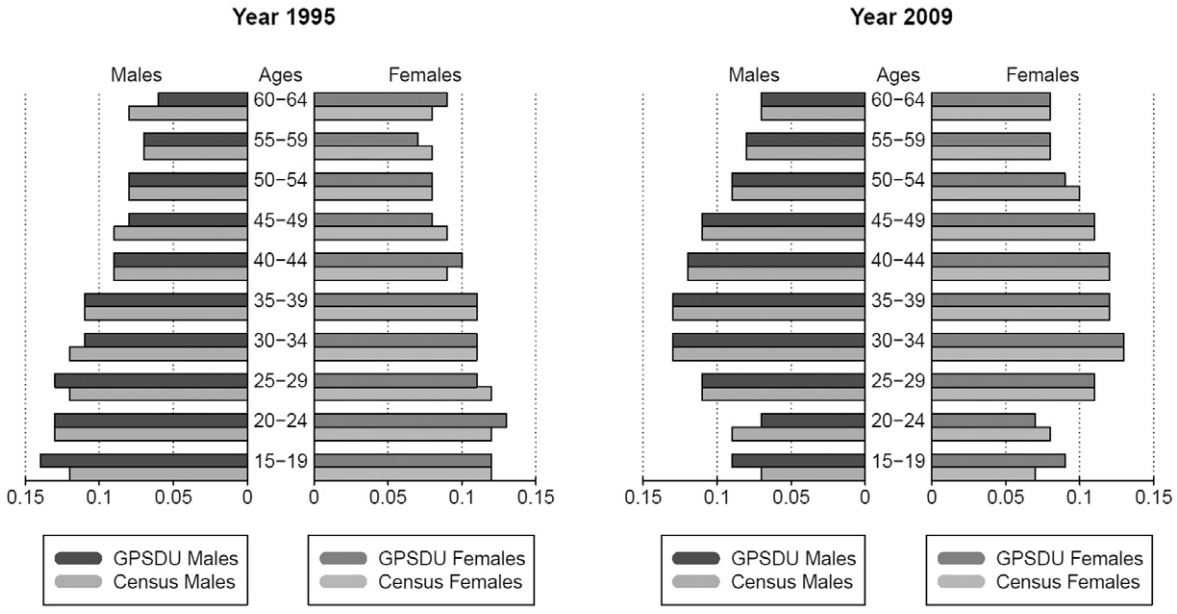

Figure A1 Spanish population pyramids for the year 1995 and 2009, both for general population surveys of drug use (GPSDU) samples and census data

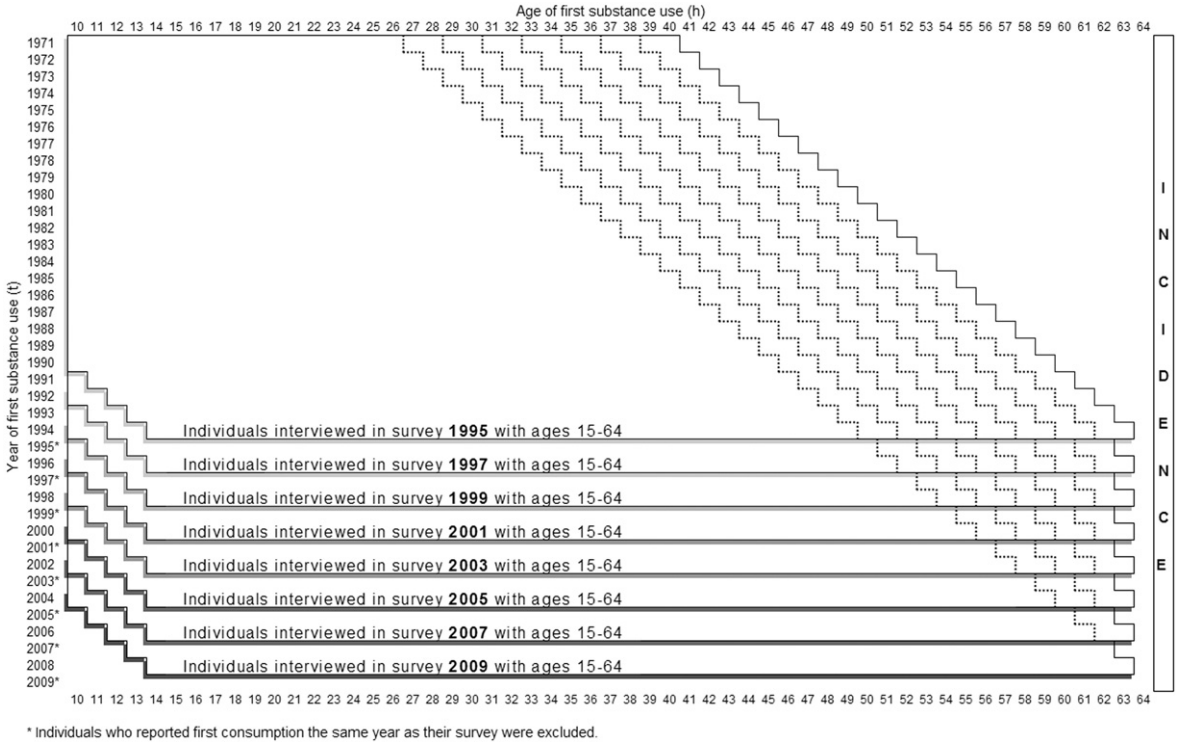

Figure A2 Eight superimposed cross-tables of calendar year by age of onset of drug use, for each biennial survey year from 1995 (top) to 2009 (bottom)

use (GPSDU) and from population census [19]. Note that the two structures are very similar, confirming the age representativeness of GPSDU samples.

APPENDIX II

Figure A2 shows the eight cross-tables from the various surveys superimposed as in a three-dimensional view. All cross-tables contain structural zeros in two subsets of cells, the bottom-left and top-right corners, corresponding to individuals with ages falling outside the survey's age range even though they are within the accepted age range of first use. For example, the top cross-table refers to individuals interviewed in the 1995 survey aged 15–64 years. From this cross-table we cannot observe individuals aged more than 40 reporting first use in 1971, as they would be aged more than 64 in the 1995 survey. Moreover, we cannot observe individuals aged less than 14 years reporting first use in 1994, as they were aged less than 15 years in the 1995 survey. In the same way, for example in the bottom cross-table, we cannot observe individuals reporting first use in 1971 older than 26 and, in 2008, under 14 years, as they would be aged more than 64 years and less than 15 years, respectively, in the 2009 survey. Note that the row marginal values of each cross-table are incidences.

While corporations dominate society and write the laws, each advance in technology is an opening for them to further restrict its users.

Richard M. Stallman

CHAPTER

9

Complementary work

9.1 Variability of incidence and lag time probability estimates. Application of the Delta method

Article 1 considered the log-linear model $log(m_{ij}) = \mu + \alpha_i + \beta_j$ for all (i, j) in a subset S of cells which is enclosed to T, the complete table of frequencies. Such model was called quasi-independence model as independence was assumed only for cells from S. Once the expected frequencies $\hat{m}_{ij}$ for all (i, j) in T were calculated, the incidence $\hat{x}_i$ and the lag time (or latency period) probabilities $\hat{\pi}_j$ were consequently estimated:

$$\hat{x}_i = \sum_{i=1,\ldots,I} \hat{m}_{ij} \tag{9.1}$$

$$\hat{\pi}_j = \sum_{h \leq j} \frac{exp(\hat{\beta}_h)}{\hat{K}}, \quad \text{where } \hat{K} = \sum_{j=1,\ldots,J} exp(\hat{\beta}_j). \tag{9.2}$$

However, the calculation of the estimates' variability is not immediate.

Log-linear model can be expressed as

$$log(m) = A \cdot \theta, \tag{9.3}$$

where $m = (m_k, k = 1, \ldots, IJ)$ is the vector of expected frequencies of dimension $(IJ) \times 1$, $\theta = (\mu, \alpha_1, \ldots, \alpha_{I-1}, \beta_1, \ldots, \beta_{J-1})$ is the vector of model parameters of dimension $(I + J - 1) \times 1$, and A matrix with 1's and 0's values corresponding to the model parameters, of dimension $(IJ) \times (I + J - 1)$.

Equation 9.1 can be expressed in matrix form as $x = Bm$ where $x = (x_i, i = 1, \ldots, I)$ and B is the matrix with 1's and 0's values of dimension $I \times (IJ)$ expressing the row marginal of table T.

The variance of x is

$$Var(x) = B \cdot Var(m) \cdot B', \tag{9.4}$$

where $Var(m) = Var(exp(A \cdot \theta))$ from 9.3.

The variance of θ is obtained when model parameters θ are estimated. However, the expression $exp(A\theta)$ is not linear, and therefore its variance cannot be obtained immediately.

We found the same problem with the variance of the lag time probabilities:

$$Var(\pi_j) = Var\left(\frac{1}{K}\sum_{h \leq j} exp(\beta_h)\right). \tag{9.5}$$

9.1.1 The multivariate Delta method

The multivariate Delta method is a procedure for obtaining the asymptotic distribution for a function of a known estimator of a given parameter θ. It is based on the following property:

Let $f(\theta)$ be a real and differentiable function of class C^1 of a vectorial parameter $\theta \in R^P$, and its first order Taylor expansion for $x \to \theta$ is:

$$f(x) = f(\theta) + (x - \theta)\left(\frac{\partial f}{\partial \theta}\right)' + o(||x - \theta||). \tag{9.6}$$

We assume $\hat{\theta}_n$ is an unbiased estimator of θ depending on a sample of size n, asymptotically converging to θ when $n \to \infty$ as follows:

$$L[\sqrt{n}(\hat{\theta}_n - \theta)] \to N(0, V(\theta)), \tag{9.7}$$

where $V(\theta)$ is the covariance matrix of $\hat{\theta}_n$.

Therefore, $f(\hat{\theta}_n)$ also converges to $f(\theta)$ asymptotically. More precisely, next convergence in law is obtained:

$$L\left[\sqrt{n}\left(f(\hat{\theta}_n) - f(\theta)\right)\right] \to N\left(0, \left(\frac{\partial f}{\partial \theta}\right) V(\theta) \left(\frac{\partial f}{\partial \theta}\right)'\right). \tag{9.8}$$

9.1.2 Application of the Delta method

Following the Delta method exposed above, the variance of incidence (equation 9.4) was calculated as follows:

$$Var(x) = B \cdot Var(exp(A \cdot \theta)) \cdot B' = B \cdot (A \cdot exp(A \cdot \theta)) Var(\theta) (A \cdot exp(A \cdot \theta))' \cdot B'. \tag{9.9}$$

The same for the variance of lag time probabilities (equation 9.5):

$$Var(\pi_j) = \left(\frac{1}{K} exp(\beta_j)\right) Var(\beta_j) \left(\frac{1}{K} exp(\beta_j)\right)'. \tag{9.10}$$

9.2 The *esindrug* package: Estimation of Incidence of Drug Use in R

The esindrug package: Estimation of Incidence of Drug Use in R

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Abstract

In drug abuse epidemiology, incidence estimation requires special statistical approaches designed to take into account inherent limitations in observed data which might lead to underestimation. A statistical method based on quasi-independence log-linear modelling which was introduced in the paper "Problematic heroin use incidence trends in Spain" has been implemented in the **esindrug** package in R. Use of this package is presented here through two example data sets obtained from drug treatment agencies in Spain and south-eastern England. Although designed with drug-abuse data in mind, the package could possibly be adapted to other contexts involving similar situations of under-reporting.

Keywords: epidemiology, incidence, drug abuse, quasi-independence, log-linear model, R .

1. Introduction

In the context of drug abuse epidemiology, incidence measures the number of persons initiating consumption of a given drug (usually heroin, cocaine, etc), per unit of time. Since illicit drug users are hidden within society, incidence is not a directly observable quantity. Therefore, we need to estimate it indirectly, based on other available information. The most useful information on drug users can be extracted from data collected routinely by Institutional Information Systems for health planning. There, valuable information such as socio-demographic data, year of first contact with the system (typically first detoxification treatment), year of drug use onset and route of administration are collected.

Incidence estimation requires special statistical methodologies designed to take into account inherent limitations in observed data which might lead to underestimation. As a consequence of the "a posteriori" method by which they are obtained, from declarations by people contact-

ing the system, data about year of onset are inevitably incomplete. There is a group of drug users who have not been observed because detailed data collection started at a point in time, when the problem manifested itself as relevant and action took place, thus the data on people who contacted the system before this time is missing. A second unobserved group is formed by those who started drug use in some past moment but have not contacted the system yet (i.e.: either they died or abandoned drug use by their own means, or will contact the system at some future moment).

The paper "Problematic heroin use incidence trends in Spain" (Sanchez-Niubo *et al.* 2009) introduced a statistical methodology based on quasi-independence log-linear modelling, adapted to the incomplete frequency tables obtained when tabulating drug use data showing the truncation pattern described above. This approach is implemented in the form of a package for the free statistical programming language and environment, R (R Development Core Team 2009). This package, called `esindrug` (Estimation of Incidence of Drug Use) has a flexible and extensible structure, in order to allow users to adapt it to their needs. The goal of the present manuscript is to document `esindrug` and show its use on a real dataset. We refer the reader to Sanchez-Niubo *et al.* (2009) for more details and further references. Moreover, in the guidelines for estimating incidence of problem drug use published by EMCDDA there is detailed information about the target population, although the methodology they employ is slightly different (Scalia Tomba *et al.* 2008).

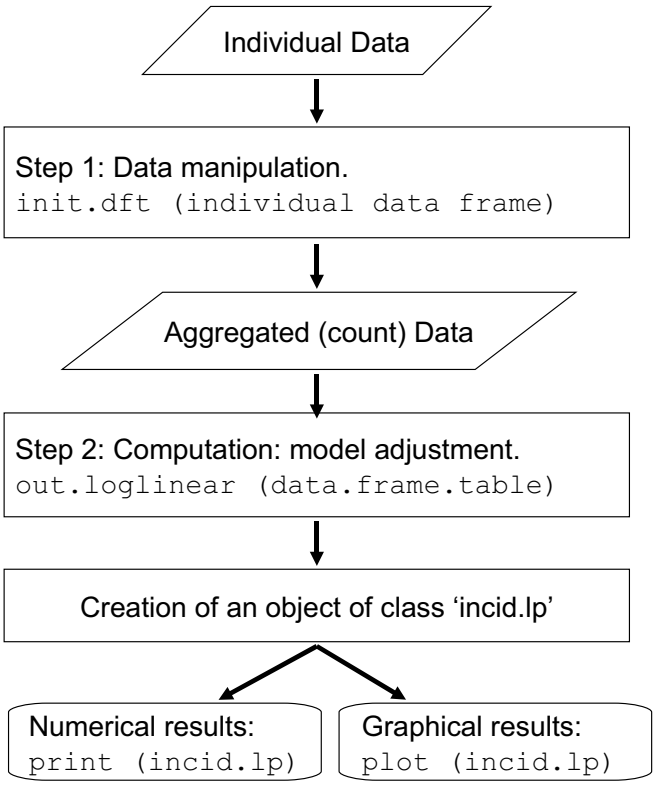
The structure of the package is summarised in section 2, while section 3 presents a practical example, including an introduction to the data (section 3.1), the procedure for calculating incidence and the latency period distribution (LPD) for the example data (section 3.2), and the comparison of different distributions proposed for fitting the log-linear model (section 3.3). Section 4 discusses a currently recognised method, known as Reporting Delay Adjustment (Hickman *et al.* 2001; Scalia Tomba *et al.* 2008), which yields identical results when used with the same database (Sanchez-Niubo *et al.* 2007).

2. Package structure

Figure 1 summarises the main steps the user must follow to obtain incidence estimates and the LPD: distribution of the time between a drug user's first consumption and their first contact with the system.

Using the package involves two main steps: firstly, function `init.dft` is used to convert data on individuals to a format appropriate for use by other functions in the package; and function `out.loglinear` supplies the incidence and LPD results. The rest of the functions in the **esindrug** package either provide support for the two main functions, or offer certain options which may or may not be of interest, depending on the needs of the user. The output can be generated as tables and/or graphics, using adaptations of the generic functions: `print` and `plot`.

Figure 1: Diagram of the main steps of the **esindrug** package



3. Practical example: the Spanish drug treatment system

3.1. The data

We demonstrate the features of this package through a data set from the Spanish Drug Observatory Register (PNSD–Plan Nacional sobre Drogas), explained in Sanchez-Niubo *et al.* (2009). 167,753 subjects were selected whose first ever treatment admission for heroin use was between 1991 and 2005 while aged from 15 to 44 years, and whose year of onset of heroin use was between 1971 and 2005 while aged from 10 to 44 years. Other variables such as gender and route of administration which could subsequently be used to evaluate specific trends and other quantities of interest, are not included in the present exercise.

The main variables are: `year.onset` as the year of heroin use onset, and `year.treat` as the year of the first ever treatment admission for heroin use. This implies the need to identify in the system if a given treatment admission was the first one ever or not, and select only the first ones. The time between these variables is called latency period (LP) and defined in the database as `lp`. If treatments other than first are selected, the calculated LP would be larger than the true value, producing a bias in the estimation of incidence. Moreover, number of calendar years of first treatment must cover a period which is "sufficiently long", according to

the substance. For example, it is known that heroin users take less time to enter detoxification treatment, counting from their first heroin use, than do users of other substances like cocaine or cannabis.

Note that `year.onset` and `year.treat` must be known for all individuals included in the database, and also there must be observations of individuals in all consecutive years of the ranges established for both these variables. For this reason, in the Spanish dataset, a few, scattered, individuals who initiated their consumption in years prior to 1971 had to be excluded.

3.2. Estimation of incidence and the LPD

Once the package is installed in the R environment, it is loaded by function `library` and documentation about it is available through the function `help`.

```
R> library(esindrug)
R> help(esindrug)
```

Data about treatment admissions for heroin use in Spain is loaded into the R environment.

```
R> data(db.h.spain)
```

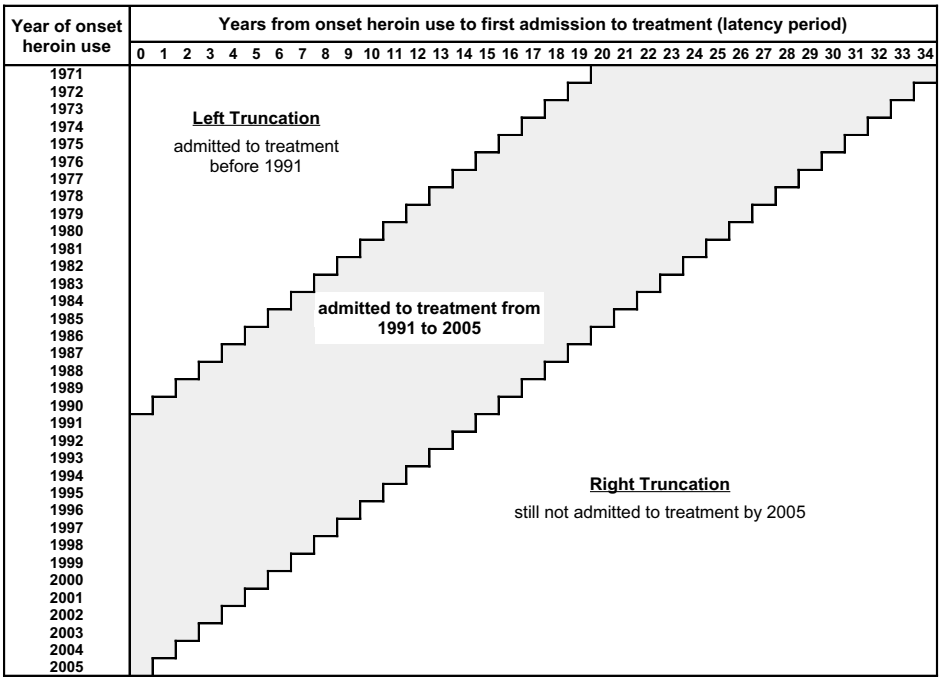
Next, we use the function `init.dft` to convert the individual data into an object with format `data.frame.table`.

```
R> dft.h.spain <- init.dft( db.h.spain$year.onset, db.h.spain$year.treat)
```

Function `init.dft` creates the variable `lp`, and then forms a table of frequencies by cross-tabulating the variable `year.onset` as rows and `lp` as columns. Attention is drawn to the two subsets of empty cells, owing to truncations, i.e. people who cannot be observed because their first treatments were or will be outside the period of observed years of treatment. In the example, left truncation, affecting people admitted to their first treatment prior to 1991, the first year observed; and right truncation, affecting people still not admitted into treatment by 2005 (see Figure 2). The function `table` from an internal R package could be used to create this observed frequency table. However, that function has the problem that empty cells are assigned zero values, when they must be missing values. Therefore, function `zeropad.miss` is called by default in the function `init.dft` to assign missing values to the truncated cells. Finally, the cross-tabulated data is converted into an R object, which in the example is called `dft.h.spain`, with format `data.frame.table`.

The object `dft.h.spain` is used as an argument in the function `out.loglinear` which uses the log-linear model approach. Another argument to be supplied when calling this function is the model to fit the data count in the log-linear model. This may be either the Poisson (P: default option), negative binomial (NB) or quasi-Poisson (QP) model, all with logarithmic link function and treatment contrast with baseline in the first level. In the example, we used the QP model as according to the results of the above mentioned paper (Sanchez-Niubo *et al.*

Figure 2: Schematic table of frequencies differentiating between the observed subset of cells and the non-observed subsets due to left and right truncations.



2009) the fit obtained with this distribution was better. How to choose the most suitable distribution is discussed in section 3.3.

```
R> out.h.spain <- out.loglinear( dft.h.spain, "QP")
```

The result, `out.h.spain`, is an object of class `incid.lp` defined as a list of three objects: `T.hat` the expected frequency table, and two data frames: `incid` the incidence results, and `lpd` the LPD. Incidence results, `out.h.spain$incid`, are initially generated as raw/absolute numbers, so a function called `rating` converts these to rates, based on Spanish population census data for the same range of ages as the incidence data (from 10 to 44).

```
R> data( census.spain)
R> rate.h.spain <- rating( out.h.spain, census.spain)
```

To see a summary of the results in a printed format, we use the generic functions `print` or `summary` with the object of class `incid.lp`, as follows:

```
R> print(out.h.spain)
Incidence results:
:    Obs Incid Estim Incid    S.E. CI -95% CI +95%
1971       108         4057 2344.58    -538    8652
1972       217         7077 4226.31   -1207   15360
1973       329         9104 3756.36    1741   16466
```

```
1974       471       11204 2939.36    5443   16965
1975       787       15807 2261.87   11374   20240
1976      1140       19232 1836.64   15632   22831
1977      1529       22000 1405.97   19245   24756
1978      2428       29918 1144.93   27674   32162
1979      2780       28863  970.22   26962   30765
1980      4756       41862  753.92   40385   43340
1981      3919       28066  743.81   26608   29524
1982      5390       32864  557.99   31771   33958
1983      5590       28144  498.15   27167   29120
1984      6530       27241  422.45   26413   28069
1985      8239       28254  387.57   27494   29013
1986      8991       24855  367.71   24134   25575
1987      9984       22175  326.80   21535   22816
1988     11540       20315  294.25   19739   20892
1989     13505       18743  284.25   18186   19300
1990     15666       17729  260.64   17218   18240
1991     12907       13766  284.86   13208   14324
1992     11267       12163  250.20   11672   12653
1993      7970        8724  233.36    8267    9182
1994      6833        7616  209.18    7206    8026
1995      5641        6423  225.72    5981    6865
1996      4443        5226  233.58    4768    5684
1997      3551        4311  234.14    3852    4770
1998      3281        4170  229.78    3719    4620
1999      2608        3511  259.87    3002    4020
2000      1846        2687  277.53    2143    3231
2001      1309        2140  301.54    1549    2731
2002       927        1788  266.78    1265    2311
2003       652        1652  400.99     866    2438
2004       502        2131  450.39    1248    3013
2005       117        1820  964.34     -70    3710

Latency Period Distribution results:
:  Latency Period   S.E. CI -95% CI +95%
0          0.0643 0.0034  0.0576  0.0710
1          0.2356 0.0056  0.2247  0.2465
2          0.3946 0.0074  0.3802  0.4091
3          0.5184 0.0091  0.5005  0.5362
4          0.6116 0.0110  0.5900  0.6332
5          0.6871 0.0129  0.6617  0.7125
6          0.7428 0.0148  0.7137  0.7718
7          0.7869 0.0171  0.7534  0.8203
8          0.8237 0.0190  0.7865  0.8608
9          0.8502 0.0214  0.8083  0.8921
10         0.8783 0.0228  0.8336  0.9229
11         0.8971 0.0242  0.8496  0.9446
```

```
12          0.9135 0.0253  0.8640  0.9631
13          0.9264 0.0262  0.8751  0.9776
14          0.9376 0.0269  0.8849  0.9903
15          0.9479 0.0274  0.8943  1.0016
16          0.9561 0.0277  0.9019  1.0104
17          0.9627 0.0279  0.9081  1.0173
18          0.9686 0.0279  0.9139  1.0233
19          0.9734 0.0279  0.9187  1.0281
20          0.9787 0.0279  0.9241  1.0333
21          0.9825 0.0278  0.9280  1.0370
22          0.9855 0.0278  0.9311  1.0399
23          0.9877 0.0277  0.9333  1.0420
24          0.9898 0.0277  0.9356  1.0441
25          0.9919 0.0276  0.9377  1.0461
26          0.9935 0.0276  0.9393  1.0476
27          0.9947 0.0276  0.9406  1.0487
28          0.9959 0.0275  0.9419  1.0499
29          0.9969 0.0275  0.9429  1.0508
30          0.9977 0.0275  0.9438  1.0516
31          0.9982 0.0275  0.9443  1.0520
32          0.9988 0.0274  0.9450  1.0526
33          0.9993 0.0274  0.9455  1.0530
34          1.0000 0.0274  0.9463  1.0537
```

Note that the standard errors and their corresponding confidence intervals are calculated by the Delta method (Bishop *et al.* 1975) through the estimated parameter from the log-linear model.

On the other hand, the graphics of incidence and the LPD can be generated using the generic function `plot` with the object of class `incid.lp`. However, there is the possibility to previously smooth the interpolation of the yearly incidence by the function `smoothing`.

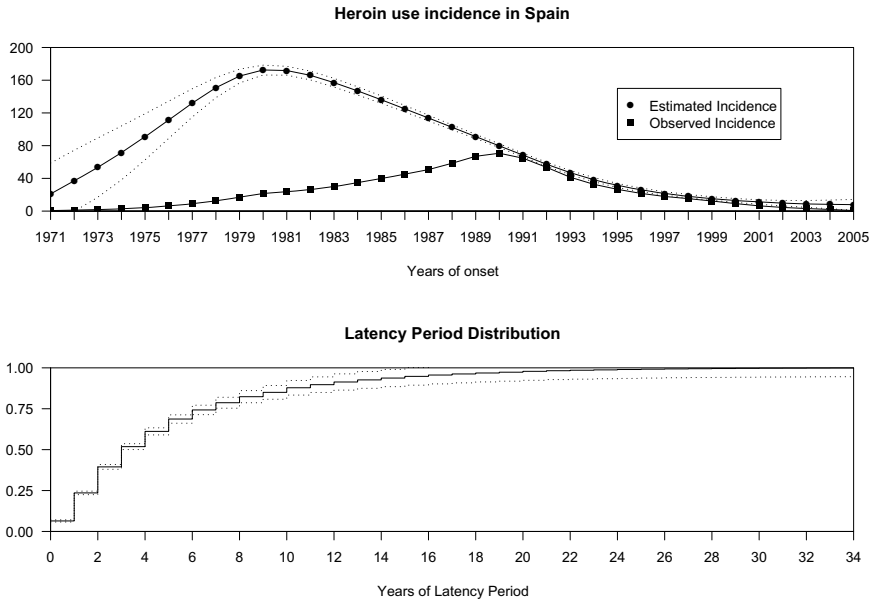
```
R> rate.smooth.h.spain <- smoothing( rate.h.spain)
```

We can see below that other useful arguments to the `plot` function are the name of the graphic (`g.tit`) and the position of the legend (`leg.x` as the x-axis position and `leg.y` the y-axis) (Figure 3).

```
R> plot( rate.smooth.h.spain, leg.x=1995, leg.y=150, g.tit= "Heroin use incidence
in Spain")
```

It is possible to generate separate graphics of incidence and LPD, by calling functions `incid.plot` and `lp.plot` separately.

Figure 3: Graphics from the function `plot` with the object `rate.smooth.h.spain` of class `incid.lp`. Spanish treatment data from 1991 to 2005.



3.3. Models to fit the data count

Using the same example database, we found that no model fitted well but, as far as we are aware, this situation is usual owing to the large cell counts and the large number of cells in the frequency table. Therefore, we consider the Pearson chi-squared which essentially compares the observed and expected frequency cells only in the observed subset of cells. To correct overdispersion, the R statistical package provides the QP model that leaves the dispersion parameter unrestricted, obtaining the same estimated parameters with larger standard errors.

Calculation of the Pearson chi-squared requires the observed and expected frequency tables, but we must first ensure that the calculation is based on only the subset of cells actually observed. This is achieved by calling function `zeropad.miss` from **esindrug** package.

Let `n` be the observed span of years of treatment, `T.obs` be the observed frequency table and `T.hat.p` and `T.hat.nb` be the expected frequency tables deriving from using Poisson and NB model, respectively :

```
R> n <- length( names( table( db.h.spain$year.treat)))
R> T.obs <- zeropad.miss( with( dft.h.spain, xtabs(Freq~years+lp)), n)
R> T.hat.p  <- zeropad.miss(as.matrix(out.loglinear(dft.h.spain, "P")$T.hat), n)
R> T.hat.nb <- zeropad.miss(as.matrix(out.loglinear(dft.h.spain,"NB")$T.hat), n)
```

And we calculate Pearson chi-squared for both of them:

```
R> chi.p <- sum(( T.obs - T.hat.p)^2 / T.hat.p, na.rm=TRUE)
R> chi.nb <- sum(( T.obs - T.hat.nb)^2 / T.hat.nb, na.rm=TRUE)
```

We find that the Poisson model gives a lower figure (6,543) for chi-squared than the NB model (8,437). Thus, Poisson fits better than the NB.

To assess overdispersion we need to calculate the dispersion parameter, `dp`. An easy way to find this is to use the function `loglinear.model` from **esindrug** package with QP model argument, as follows:

```
R> dp <- summary( loglinear.model(dft.h.spain, F.d="QP"))$dispersion
```

If the dispersion parameter was near to 1, we could just use the Poisson model. In our case, the dispersion parameter is greater than 1 (18.6), so the QP model fits the Poisson model's overdispersion.

4. Reporting Delay Adjustment (RDA) method

The RDA method was previously proposed to estimate incidence of drug use (Hickman *et al.* 2001; Scalia Tomba *et al.* 2008). In comparison with the log-linear model approach, RDA can only estimate incidence for the same period of years for which treatment admissions were observed. In other words, it can only solve the right truncation explained in section 3.2. In the case of Spanish data, it would only be possible to estimate incidence of heroin use for the period from 1991 to 2005 and from 0 to 14 years of LP. If we draw the table of frequencies which results from limiting to these years of onset, we observe that it is a sub-table of the table of frequencies from Figure 2. The LPD resulting from both approaches, RDA and log-linear model, is the same (Brookmeyer and Damiano 1989) and provides the same incidence results in the same sub-table of frequencies (Sanchez-Niubo *et al.* 2007). Therefore, the `esindrug` package can be used to estimate incidence of drug use when using the same situation as that for which the RDA method is applicable.

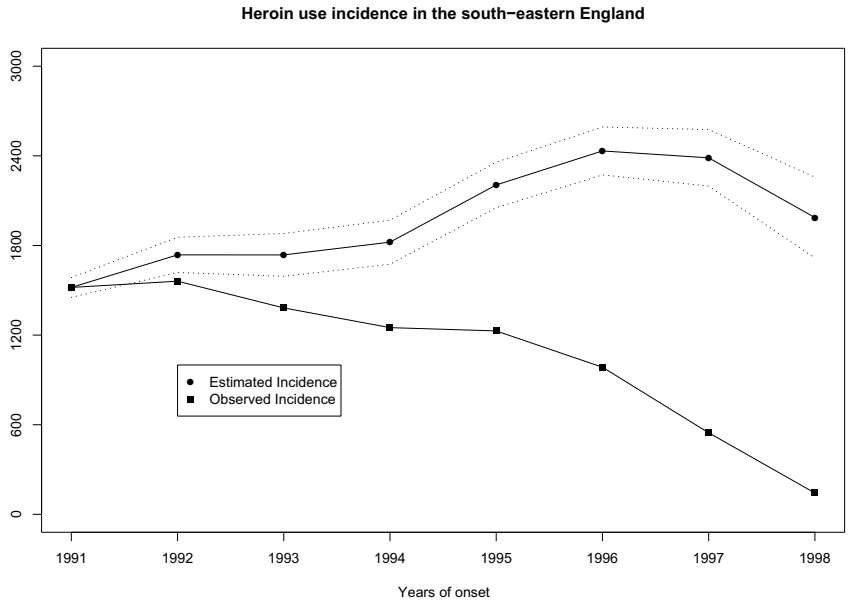
The data extracted from Hickman's paper (Hickman *et al.* 2001) was also used to estimate incidence of heroin use through the `esindrug` package using the log-linear model approach. This data is included in the package directly as a data frame table:

```
R> data(dft.hickman)
```

And using the following instructions,

```
R> out.hickman <- out.loglinear( dft.hickman)
R> incid.plot(out.hickman,ylim=c(0,3000), leg.y=1000,
g.tit="Heroin use incidence in the south-eastern England", max.x=3000)
```

Figure 4: Graphic of heroin use incidence in the south-eastern England. Data extracted from Hickman *et al.* (2001).




```
R> round(out.hickman$lp,4)
:  Latency Period   S.E. CI -95% CI +95%
0         0.0720 0.0025  0.0671  0.0768
1         0.2288 0.0038  0.2212  0.2363
2         0.4049 0.0052  0.3948  0.4150
3         0.5569 0.0066  0.5438  0.5699
4         0.6860 0.0087  0.6690  0.7030
5         0.7957 0.0113  0.7737  0.8178
6         0.8986 0.0146  0.8701  0.9272
7         1.0000 0.0196  0.9615  1.0385
```

We observe in Figure 4 and the listing produced by `out.hickman$lp` that the results are identical to those published by Hickman, although the standard errors are slightly different because we used different methods (bootstrapping vs. Delta method).

5. Discussion

Spanish treatment admission data is being constantly updated, and other countries have similar series of data. This package provides a tool permitting immediate application of the statistical methodology to such series of data, so that results may be obtained quickly. The package is released under a General Public License (GPL), and incorporates detailed

complementary help. Although designed with drug-abuse data in mind, it could possibly be adapted to other contexts involving similar situations of under-reporting.

The log-linear model approach, when used in its complete version, requires fitting a large number of missing cells. Thus, it is worth considering the size of the database. It needs to cover a time span large enough to include a high proportion of the LP of the substance under study (different substances have different LP's) and, at the same time, enough subjects are needed to have a continuum in the scale of years of onset according to LP.

The log-linear model used in the package is based on a hypothesis of quasi-independence (independence among the set of observed cells), i.e. that estimates generated by the model are conditioned to the years of onset of consumption being independent of the LP. In other words, it is assumed that the LPD is the same for all points in time. This assumption must be taken into account when interpreting the incidence results, and contrasted with the history of consumption in the geographical setting under study. For example, in Spain methadone programs were extended to include all drug detoxification treatment centres after 1991, representing an important change in treatment availability. The implications of this change are discussed in the reference article (Sanchez-Niubo *et al.* 2009).

The package is still under development at the time of writing, and future versions may include statistical methods which we are currently working on to solve some of these problems.

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Scalia Tomba GP, Rossi C, Taylor C, Klempova D, Wiessing L (2008). *Guidelines for Estimating the Incidence of Problem Drug Use.* EMCDDA, Lisbon.

Article written in 2009
R Package can be found in the following public address:
https://intranet.fimim.cat/arxiuspersones/showsharedfiles?id=3796

9.3 Row-Column association model: estimation of parameters

We consider an $I \times J$ contingency table that cross-classifies a multinomial sample of n subjects on two categorical responses. The cell probabilities are π_{ij} and the expected frequencies are $\mu_{ij} = n\pi_{ij}$. We assume Poisson sampling for $N = IJ$ independent cell counts n_{ij} having $\mu_{ij} = E(n_{ij})$. Actually observed cell count values will also be denoted by n_{ij}, except when ambiguity may arise.

9.3.1 Row and column effects model

As said in section 4.1.3, we consider the following RC(1) model:

$$\log(\mu_{ij}) = \gamma + a_i + b_j + \phi u_i v_j, \quad i = 1, \ldots, I; j = 1, \ldots, J. \tag{9.11}$$

Parameter ϕ is the *intrinsic association*, while a_i and u_i represent row effects and, b_j and v_j column effects. The constraints imposed upon the parameters for identifiability reasons, are

$$\sum_{i=1}^{I} a_i = \sum_{j=1}^{J} b_j = 0, \tag{9.12}$$

$$\sum_{i=1}^{I} u_i = \sum_{j=1}^{J} v_i = 0, \tag{9.13}$$

$$\sum_{i=1}^{I} u_i^2 = \sum_{j=1}^{J} v_i^2 = 1. \tag{9.14}$$

9.3.2 Estimation of parameters

We consider the Poisson log-likelihood function:

$$\ell(\theta) = \sum_{i=1}^{I} \sum_{j=1}^{J} \ell_{ij}, \tag{9.15}$$

where

$$\ell_{ij} = n_{ij} \log[\mu_{ij}(\theta)] - \mu_{ij}(\theta), \quad 1 \leq i \leq I, \quad 1 \leq j \leq J, \tag{9.16}$$

and

$$\theta = (\gamma, a_1, \ldots, a_I, b_1, \ldots, b_J, \phi, u_1, \ldots, u_I, v_1, \ldots, v_J)$$

is the set of model parameters, with length $2(I + J) + 2$.

9.3.2.1 **Reparametrization**

Firstly, we reparametrize the RC model incorporating the restrictions 9.12 and 9.13 into the model. For instance, we replace parameter a, subjected to the restriction $\sum_{i=1}^{I} a_i = 0$, with the new parameter $\alpha = (\alpha_2, \ldots, \alpha_I)$ (note there is no α_1) defined by:

$$\begin{array}{l} a_1 = a_1 + 0 \\ a_2 = a_1 + \alpha_2 \\ \ldots\ldots\ldots\ldots\ldots\ldots \\ a_I = a_1 + \alpha_I \\ \hline 0 = I a_1 + \sum_{i=2}^{I} \alpha_i \end{array}$$

$$\begin{array}{l} a_1 = 0 + 0 = \frac{-1}{I} \sum_{i=2}^{I} \alpha_i + 0 = A_1 \alpha \\ a_2 = a_1 + \alpha_2 = \frac{-1}{I} \sum_{i=2}^{I} \alpha_i + \alpha_2 = A_2 \alpha \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ a_I = 0 + 0 = 0 + 0 = A_I \alpha \end{array}$$

In matrix form:

$$a = A \cdot \alpha,$$

where

$$A_{I \times (I-1)} = \begin{pmatrix} \frac{-1}{I} & \frac{-1}{I} & \cdots & \frac{-1}{I} \\ 1 - \frac{-1}{I} & \frac{-1}{I} & \cdots & \frac{-1}{I} \\ \frac{-1}{I} & 1 - \frac{-1}{I} & \cdots & \frac{-1}{I} \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \frac{-1}{I} & \frac{-1}{I} & \cdots & 1 - \frac{-1}{I} \end{pmatrix}$$

Note that A is the result of discarding column 1 in the $I \times I$ *centering matrix* , where I is the $I \times I$ identity matrix and $\mathbf{1}$ is the $I \times 1$ column vector whose entries are all equal to 1. For ease of notation we keep columns in A labelled 2 to J.

Therefore,

$$a_i = \sum_{k=2}^{I} A_{ik} \Delta \alpha_k, \quad \text{where } i = 1, \ldots, I. \tag{9.17}$$

Similarly, let B be the $J \times (J-1)$ matrix obtained by discarding column 1 in the $J \times J$ *centering matrix*. Then:

$$b_j = \sum_{k=2}^{J} B_{jk} \beta_k, \quad u_i = \sum_{k=2}^{I} A_{ik} \xi_k, \quad \text{and } v_j = \sum_{k=2}^{J} B_{jk} \zeta_k.$$

Restriction (9.14) will not be implemented as a reparametrized model, it will be managed by renormalizing in each iteration of the estimating procedure.

From now on θ will denote the list of new parameters,

$$\theta = (\gamma, \alpha_2, \ldots, \alpha_I, \beta_2, \ldots, \beta_J, \phi, \xi_2, \ldots, \xi_I, \zeta_2, \ldots, \zeta_J),$$

with length $2(I+J)-2$.

9.3.3 Maximum Likelihood Estimation

To estimate parameters Newton's method approach has been considered: .

9.3.3.1 Newton's method

This method is used to find successively better approximations to a maximum of the log-likekihood function, by using the following algorithm:

$$\theta^{(t+1)} = \theta^{(t)} - H_\theta^{-1}\frac{d\ell}{d\theta}, \tag{9.18}$$

where $H_\theta = \dfrac{\partial^2 \ell}{\partial \theta^2}$ is the Hessian matrix.

9.3.3.2 Derivatives of the log-likelihood function

The derivative of ℓ_{ij} with respect to a given component θ_t of θ is:

$$\frac{\partial \ell_{ij}}{\partial \theta_k} = \frac{\partial \ell_{ij}}{\partial \mu_{ij}} \cdot \frac{\partial \mu_{ij}}{\partial \theta_k} = (-1 + \frac{n_{ij}}{\mu_{ij}}) \cdot \frac{\partial \mu_{ij}}{\partial \theta_k} =$$

$$= (-\mu_{ij} + n_{ij}) \cdot \frac{1}{\mu_{ij}} \frac{\partial \mu_{ij}}{\partial \theta_k} = (-\mu_{ij} + n_{ij}) \cdot \frac{\partial log(\mu_{ij})}{\partial \theta_k}.$$

As $\log(\mu_{ij}) = \gamma + a_i + b_j + \phi u_i v_j$:

$$\begin{aligned}
\frac{\partial \ell_{ij}}{\partial \gamma} &= n_{ij} - \mu_{ij} \\
\frac{\partial \ell_{ij}}{\partial \alpha_r} &= (n_{ij} - \mu_{ij})\frac{\partial a_i}{\partial \alpha_r} = (n_{ij} - \mu_{ij})A_{ir} \\
\frac{\partial \ell_{ij}}{\partial \beta_s} &= (n_{ij} - \mu_{ij})\frac{\partial b_j}{\partial \beta_s} = (n_{ij} - \mu_{ij})B_{js} \\
\frac{\partial \ell_{ij}}{\partial \phi} &= (n_{ij} - \mu_{ij})\frac{\partial \phi u_i v_j}{\partial \phi} = (n_{ij} - \mu_{ij}) \textstyle\sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l) \\
\frac{\partial \ell_{ij}}{\partial \xi_r} &= (n_{ij} - \mu_{ij})\frac{\partial \phi u_i v_j}{\partial \xi_r} = (n_{ij} - \mu_{ij})A_{ir}\phi \textstyle\sum_{l=2}^{J}(B_{jl}\zeta_l) \\
\frac{\partial \ell_{ij}}{\partial \zeta_s} &= (n_{ij} - \mu_{ij})\frac{\partial \phi u_i v_j}{\partial \zeta_s} = (n_{ij} - \mu_{ij}) \textstyle\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi
\end{aligned}$$

9.3.3.3 **Second derivatives of the log-likelihood function. The Hessian matrix.**

Second derivative of the log-likelihood function for any component of θ is:

$$\frac{\partial^2 \ell_{ij}}{\partial\theta_r \partial\theta_s} = \frac{\partial}{\partial\theta_r}\left(\frac{\partial \ell_{ij}}{\partial\theta_s}\right)$$

Hessian components:

$$\begin{aligned}
\frac{\partial^2 \ell_{ij}}{\partial\gamma\partial\gamma} &= \frac{\partial}{\partial\gamma}(n_{ij}-\mu_{ij}) && = -\mu_{ij}\\
\frac{\partial^2 \ell_{ij}}{\partial\gamma\partial\alpha_r} &= \frac{\partial}{\partial\gamma}(n_{ij}-\mu_{ij})A_{ir} && = -\mu_{ij}A_{ir}\\
\frac{\partial^2 \ell_{ij}}{\partial\gamma\partial\beta_s} &= \frac{\partial}{\partial\gamma}(n_{ij}-\mu_{ij})B_{js} && = -\mu_{ij}B_{js}\\
\frac{\partial^2 \ell_{ij}}{\partial\gamma\partial\phi} &= \frac{\partial}{\partial\gamma}(n_{ij}-\mu_{ij})\sum_{k=2}^{I}(A_{ik}\xi_k)\sum_{l=2}^{J}(B_{jl}\zeta_l) && = -\mu_{ij}\sum_{k=2}^{I}(A_{ik}\xi_k)\sum_{l=2}^{J}(B_{jl}\zeta_l)\\
\frac{\partial^2 \ell_{ij}}{\partial\gamma\partial\xi_r} &= \frac{\partial}{\partial\gamma}(n_{ij}-\mu_{ij})A_{ir}\phi\sum_{l=2}^{J}(B_{jl}\zeta_l) && = -\mu_{ij}A_{ir}\phi\sum_{l=2}^{J}(B_{jl}\zeta_l)\\
\frac{\partial^2 \ell_{ij}}{\partial\gamma\partial\zeta_s} &= \frac{\partial}{\partial\gamma}(n_{ij}-\mu_{ij})\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi && = -\mu_{ij}\sum_{k=2}^{J}(A_{ik}\xi_k)B_{js}\phi
\end{aligned}$$

$$\begin{aligned}
\frac{\partial^2 \ell_{ij}}{\partial\alpha_r\partial\alpha_{r'}} &= \frac{\partial}{\partial\alpha_r}(n_{ij}-\mu_{ij})A_{ir'} = \sum_{i'}\frac{\partial}{\partial a_{i'}}\frac{\partial a_{i'}}{\partial\alpha_r}(n_{ij}-\mu_{ij})A_{ir'}\\
&= \sum_{i'}A_{i'r}\frac{\partial}{\partial a_{i'}}(n_{ij}-\mu_{ij})A_{ir'} = \sum_{i'}A_{i'r}(-\mu_{ij}\cdot\delta_{ii'})A_{ir'}\\
&= -\mu_{ij}A_{ir}A_{ir'}.
\end{aligned}$$

$$\frac{\partial^2 \ell_{ij}}{\partial \alpha_r \partial \beta_s} = \frac{\partial}{\partial \alpha_r}(n_{ij} - \mu_{ij})B_{js} = \sum_{i'} \frac{\partial}{\partial a_{i'}} \frac{\partial a_{i'}}{\partial \alpha_r}[(n_{ij} - \mu_{ij})B_{js}]$$

$$= \sum_{i'} A_{i'r} \frac{\partial}{\partial a_{i'}}(n_{ij} - \mu_{ij})B_{js} = \sum_{i'} A_{i'r}(-\mu_{ij} \cdot \delta_{ii'})B_{js} = -\mu_{ij}A_{ir}B_{js}$$

$$\frac{\partial^2 \ell_{ij}}{\partial \alpha_r \partial \phi} = \frac{\partial}{\partial \alpha_r}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{i'} \frac{\partial}{\partial a_{i'}} \frac{\partial a_{i'}}{\partial \alpha_r}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{i'} A_{i'r} \frac{\partial}{\partial a_{i'}}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{i'} A_{i'r}(-\mu_{ij} \cdot \delta_{ii'}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= -\mu_{ij}A_{ir} \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$\frac{\partial^2 \ell_{ij}}{\partial \alpha_r \partial \xi_{r'}} = \frac{\partial}{\partial \alpha_r}(n_{ij}-\mu_{ij})A_{ir'}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l) = \sum_{i'} \frac{\partial}{\partial a_{i'}}\frac{\partial a_{i'}}{\partial \alpha_r}(n_{ij}-\mu_{ij})A_{ir'}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{i'} A_{i'r}\frac{\partial}{\partial a_{i'}}(n_{ij}-\mu_{ij})A_{ir'}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l) = \sum_{i'} A_{i'r}(-\mu_{ij}\cdot\delta_{ii'})A_{ir'}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= -\mu_{ij}A_{ir}A_{ir'}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$\frac{\partial^2 \ell_{ij}}{\partial \alpha_r \partial \zeta_s} = \frac{\partial}{\partial \alpha_r}(n_{ij}-\mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi = \sum_{i'} \frac{\partial}{\partial a_{i'}}\frac{\partial a_{i'}}{\partial \alpha_r}(n_{ij}-\mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi$$

$$= \sum_{i'} A_{i'r}\frac{\partial}{\partial a_{i'}}(n_{ij}-\mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi = \sum_{i'} A_{i'r}(-\mu_{ij}\cdot\delta_{ii'}) \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi$$

$$= -\mu_{ij}A_{ir}B_{js}\phi \sum_{k=2}^{I}(A_{ik}\xi_k)$$

$$\frac{\partial^2 \ell_{ij}}{\partial \beta_s \partial \beta_{s'}} = \frac{\partial}{\partial \beta_s}(n_{ij}-\mu_{ij})B_{js'} = \sum_{j'} \frac{\partial}{\partial b_{j'}}\frac{\partial b_{j'}}{\partial \beta_s}(n_{ij}-\mu_{ij})B_{js'}$$

$$= \sum_{j'} B_{j's}\frac{\partial}{\partial b_{j'}}(n_{ij}-\mu_{ij})B_{js'} = \sum_{j'} B_{j's}(-\mu_{ij}\cdot\delta_{jj'})B_{js'} = -\mu_{ij}B_{js}B_{js'}$$

$$\frac{\partial^2 \ell_{ij}}{\partial \beta_s \partial \phi} = \frac{\partial}{\partial \beta_s}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{j'} \frac{\partial}{\partial b_{j'}} \frac{\partial b_{j'}}{\partial \beta_s}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{j'} B_{j's} \frac{\partial}{\partial b_{j'}}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{j'} B_{j's}(-\mu_{ij} \cdot \delta_{jj'}) \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= -\mu_{ij} B_{js} \sum_{k=2}^{I}(A_{ik}\xi_k) \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$\frac{\partial^2 \ell_{ij}}{\partial \beta_s \partial \xi_r} = \frac{\partial}{\partial \beta_s}(n_{ij} - \mu_{ij}) A_{ir}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l) = \sum_{j'} \frac{\partial}{\partial b_{j'}} \frac{\partial b_{j'}}{\partial \beta_s}(n_{ij} - \mu_{ij}) A_{ir}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{j'} B_{j's} \frac{\partial}{\partial b_{j'}}(n_{ij} - \mu_{ij}) A_{ir}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l) = \sum_{j'} B_{j's}(-\mu_{ij} \cdot \delta_{jj'}) A_{ir}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= -\mu_{ij} B_{js} A_{ir}\phi \sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$\frac{\partial^2 \ell_{ij}}{\partial \beta_s \partial \zeta_{s'}} = \frac{\partial}{\partial \beta_s}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) B_{js'}\phi = \sum_{j'} \frac{\partial}{\partial b_{j'}} \frac{\partial b_{j'}}{\partial \beta_s}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I}(A_{ik}\xi_k) B_{js'}\phi$$

$$= \sum_{j'} B_{j's} \frac{\partial}{\partial b_{j'}} (n_{ij} - \mu_{ij}) \sum_{k=2}^{I} (A_{ik}\xi_k) B_{js'}\phi = \sum_{j'} B_{j's}(-\mu_{ij} \cdot \delta_{jj'}) \sum_{k=2}^{I} (A_{ik}\xi_k) B_{js'}\phi$$

$$= -\mu_{ij} B_{js} B_{js'} \phi \sum_{k=2}^{I} (A_{ik}\xi_k)$$

$$\frac{\partial^2 \ell_{ij}}{\partial\phi\partial\phi} = \frac{\partial}{\partial\phi}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I} (A_{ik}\xi_k) \sum_{l=2}^{J} (B_{jl}\zeta_l)$$

$$= \sum_{k=2}^{I} (A_{ik}\xi_k) \sum_{l=2}^{J} (B_{jl}\zeta_l)(-\mu_{ij}u_i v_j) = \sum_{k=2}^{I} (A_{ik}\xi_k) \sum_{l=2}^{J} (B_{jl}\zeta_l) \left(-\mu_{ij} \sum_{k=2}^{I} (A_{ik}\xi_k) \sum_{l=2}^{J} (B_{jl}\zeta_l) \right)$$

$$= -\mu_{ij} \left[\sum_{k=2}^{I} (A_{ik}\xi_k) \sum_{l=2}^{J} (B_{jl}\zeta_l) \right]^2$$

$$\frac{\partial^2 \ell_{ij}}{\partial\phi\partial\xi_r} = \frac{\partial}{\partial\phi}(n_{ij} - \mu_{ij}) A_{ir}\phi \sum_{l=2}^{J} (B_{jl}\zeta_l) = A_{ir} \sum_{l=2}^{J} (B_{jl}\zeta_l) \frac{\partial}{\partial\phi}\phi(n_{ij} - \mu_{ij})$$

$$= A_{ir} \sum_{l=2}^{J} (B_{jl}\zeta_l) \left[(n_{ij} - \mu_{ij}) + \phi(-\mu_{ij}u_i v_j) \right]$$

$$= A_{ir} \sum_{l=2}^{J} (B_{jl}\zeta_l) \left[(n_{ij} - \mu_{ij}) + \phi(-\mu_{ij} \sum_{k=2}^{I} (A_{ik}\xi_k) \sum_{l=2}^{J} (B_{jl}\zeta_l)) \right]$$

$$\frac{\partial^2 \ell_{ij}}{\partial\phi\partial\zeta_s} = \frac{\partial}{\partial\phi}(n_{ij}-\mu_{ij})\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi = \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\frac{\partial}{\partial\phi}\phi(n_{ij}-\mu_{ij})$$

$$= \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\left[(n_{ij}-\mu_{ij})+\phi(-\mu_{ij}u_iv_j)\right]$$

$$= \sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\left[(n_{ij}-\mu_{ij})+\phi(-\mu_{ij}\sum_{k=2}^{I}(A_{ik}\xi_k)\sum_{l=2}^{J}(B_{jl}\zeta_l))\right]$$

$$\frac{\partial^2 \ell_{ij}}{\partial\xi_r\partial\xi_{r'}} = \frac{\partial}{\partial\xi_r}(n_{ij}-\mu_{ij})A_{ir'}\phi\sum_{l=2}^{J}(B_{jl}\zeta_l) = \sum_{i'}\frac{\partial}{\partial u_{i'}}\frac{\partial u_{i'}}{\partial\xi_r}(n_{ij}-\mu_{ij})A_{ir'}\phi\sum_{l=2}^{J}(B_{jl}\zeta_l)$$

$$= \sum_{i'}A_{i'r}\frac{\partial}{\partial u_{i'}}(n_{ij}-\mu_{ij})A_{ir'}\phi\sum_{l=2}^{J}(B_{jl}\zeta_l) = \sum_{i'}A_{i'r}(-\mu_{ij}\cdot\delta_{ii'}\phi v_j)A_{ir'}\phi\sum_{l=2}^{J}(B_{jl}\zeta_l) =$$

$$= -\mu_{ij}A_{ir}A_{ir'}\left[\phi\sum_{l=2}^{J}(B_{jl}\zeta_l)\right]^2$$

$$\frac{\partial^2 \ell_{ij}}{\partial\xi_r\partial\zeta_s} = \frac{\partial}{\partial\xi_r}(n_{ij}-\mu_{ij})\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi = \sum_{i'}\frac{\partial}{\partial u_{i'}}\frac{\partial u_{i'}}{\partial\xi_r}(n_{ij}-\mu_{ij})\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi$$

$$= \sum_{i'}A_{i'r}\frac{\partial}{\partial u_{i'}}(n_{ij}-\mu_{ij})\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi = \sum_{i'}A_{i'r}(-\mu_{ij}\cdot\delta_{ii'}\phi u_i)\sum_{k=2}^{I}(A_{ik}\xi_k)B_{js}\phi$$

$$= -\mu_{ij} A_{ir} B_{js} \left[\phi \sum_{k=2}^{I} (A_{ik}\xi_k) \right]^2$$

$$\frac{\partial^2 \ell_{ij}}{\partial \zeta_s \partial \zeta_{s'}} = \frac{\partial}{\partial \zeta_s}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I} (A_{ik}\xi_k) B_{js'}\phi = \sum_{j'} \frac{\partial}{\partial v_{j'}} \frac{\partial v_{j'}}{\partial \xi_r}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I} (A_{ik}\xi_k) B_{js'}\phi$$

$$= \sum_{j'} B_{j's} \frac{\partial}{\partial v_{j'}}(n_{ij} - \mu_{ij}) \sum_{k=2}^{I} (A_{ik}\xi_k) B_{js'}\phi = \sum_{j'} B_{j's}(-\mu_{ij} \cdot \delta_{jj'}\phi u_i) \sum_{k=2}^{I} (A_{ik}\xi_k) B_{js'}\phi$$

$$= -\mu_{ij} B_{js} B_{js'} \left[\phi \sum_{k=2}^{I} (A_{ik}\xi_k) \right]^2$$

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Declaration

I herewith declare that I have produced this work without the prohibited assistance of third parties and without making use of aids other than those specified; notions taken over directly or indirectly from other sources have been identified as such. This work has not previously been presented in identical or similar form to any examination board.

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