1. Introduction

In recent years, cardiovascular diseases (CVD) contributed to 42% of overall mortality in the European Union, according to the 2008 edition of the European cardiovascular disease statistics (European Heart Network, 2008). Over a third of deaths from CVD are from coronary heart disease and just over a quarter are from cerebrovascular disease (stroke). Standardized death rates for heart disease have fallen dramatically in the last 25 years in western Europe, both for men and for women. For example, since the 1970s, coronary heart disease mortality in England has fallen by a remarkable 60%, and by approximately 6% every year between 2000 and 2007 (M. Bajekal et al., 2012). The situation has also improved more recently in central Europe (Zatonski and Bhala, 2012). Trends are however still much less favourable in the eastern part of Europe, Ukraine, Belarus and Russia. For instance, in Belarus trends in standardized CVD death rates increased, especially for males, until the end of the 1990s; they are slightly declining since (Grigoriev, 2012).

How do these levels and trends in mortality relate to those in morbidity? Unfortunately, most diseases are not routinely recorded even in the developed countries, with the exception of some transmissible diseases such as tuberculosis. For a thorough evaluation of the various sources of morbidity data in Europe, see Gourbin (1997). An important source of information
on cardiovascular diseases has been the MONICA Project set up under the auspices of WHO. The MONICA Project was established in the early 1980s in various centres around the world to monitor trends in cardiovascular diseases and to relate these to risk factor changes in the population over a ten year period. The present paper will recall the main characteristics of the MONICA Project, and then examine as a case study the MONICA-BELLUX Register which has been set up in the Province of Luxembourg in Belgium. The paper will present some results drawn from the MONICA Project and its MONICA-BELLUX offshoot. It will end with a discussion of the pros and cons of this type of data collection tool.

2. The MONICA Project

The MONICA (Multinational MONI-toring of trends and determinants in CArdiovascular disease) Project was established under the auspices of WHO to monitor trends in cardiovascular diseases, and to relate these to risk factor changes in e.g. daily living or health care, in defined communities in different countries, over a ten year period. It was set up to explain the diverse trends in cardiovascular disease mortality which were observed from the 1970s onwards. There were a total of 37 MONICA Collaborating Centres in 21 countries (including 29 populations in 16 European countries). The ten year data collection was completed in the late 1990s, though several Centres are still active today. However, as stated in European Heart Network (2008, p.37), “patterns of CHD incidence and case fatality across Europe may have changed since the mid 1990s. Furthermore, the definition of myocardial infarction (heart attack) has changed following the introduction of troponin estimations which have increased the ability to detect myocardial infarction».

According to the MONICA Manual published by the WHO MONICA Project and available online (http://www.ktl.fi/publications/monica/manual/index.htm), four basic sources of information were to be utilized in the core study over a period of 10 years, three involving special studies:

1. Routinely available administrative data on the study population, from local government and local medical sources.
2. Investigation of medically recognized cardiovascular events, fatal and non-fatal, using medical and medico-legal sources and validating the original diagnoses using MONICA criteria.
3. Continuous or intermittent monitoring of the acute care of coronary and stroke events.
4. Population surveys to monitor levels of risk factors and health-related behaviour.

The following description is mostly based on the monograph published by WHO (Tunstall-Pedoe (ed.), 2003), to which the reader is referred. Changes in cardiovascular mortality rates can be related to a change in disease incidence, or a change in case fatality, or changes in both disease incidence and case fatality. The MONICA Project therefore involved the measurement of both incidence rates and case fatality rates. Case fatality is defined by the MONICA project as dying within 28 days of a coronary event. The Centres were also to monitor risk factor levels and trends, and medical care. One should note that the term ‘incidence rate’ strictly means in epidemiology the rate at which disease occurs in individuals previously free of the disease. It was however not possible in the MONICA studies to have information on the disease-free population, and the population of the area concerned has been used instead. Angina pectoris was not included in incidence, which was confined to the major acute coronary events of myocardial infarction and coronary death. Stroke registration was officially ‘core’ in the objectives of the project but in practice became ‘optional’. Actually, fewer than half of the MONICA centres participated in the stroke component of the MONICA Project. This was largely due to the fact that diagnosis of stroke at that time was based entirely on clinical symptoms and signs, and thus not very reliable. Nowadays, modern imaging techniques help in deciding if stroke (brain infarct or intracerebral haemorrhage) has occurred.

MONICA Centres were responsible for undertaking registration of all coronary events within defined age groups (25–shifted later on to 35 – to 64 years of age) in both sexes over a period of ten years. Population risk-factor surveys were to be conducted at least at the beginning and at the end of this period, and optionally in the middle. Coronary care was also to be monitored at least at the beginning and at the end of the period. For fatal cases, because coronary deaths are often sudden and occurring outside hospital, notification usually occurred when the victim was already dead. The notification and investigation of fatal cases usually involved access to death certificates. For non-fatal cases, the latter can be identified through hospital services, or possibly from cardiologists and general practitioners in private-practice. More practical details on the procedure are given in section 3 dealing with the MONICA- BELLUX register.

As an example of the results of the project, Figure 1 presents the coronary-event incidence rates for the final three years of registration, ending in the mid-1990’s, drawn from the various
MONICA registers. Rates are computed using registration data for events and demographic data for population denominators. Results are age-standardized for the 35–64 age group, using the WHO world standard population. Coronary events are defined using MONICA diagnostic criteria, incorporating definite non-fatal myocardial infarction and definite, possible and unclassifiable coronary deaths. One observes the dramatic differences between populations of the same sex and the high toll for males compared to females. In particular, one notices for Belgium, at that time, the poor ranking of both males and females from the Charleroi register (BEL-CHA) and the much better situation of those from Ghent (BEL-GHE). A recent summary of the major findings of the MONICA project, with a discussion, can be found for example in Luepker (2011).

Figure 1. Age-standardized coronary event incidence rates (ages 35-64):
final three years of registration

Source: Luepker (2011)

Though considered as a former MONICA Collaborating Centre (MCC 14), the MONICA-BELLUX register is not included in this final data set because – according to Tunstall-Pedoe (ed.) (2003, p. 127) – “after several years of collaboration, data stopped coming to the Data Centre” in Helsinki. Actually, due to a lack of funding, BELLUX was unfortunately unable to organize the 2nd and 3rd population surveys required by the MONICA protocol. In a previous publication based on the MONICA Project, the Province of Luxembourg had a coronary event rate in between that of Charleroi and Ghent (Tunstall-Pedoe et al., 1994).

3. The MONICA-BELLUX Register

3.1 Data collection
The BELLUX register was set up in 1983 in the Belgian Province of Luxembourg as a MONICA Collaborating Centre, with Dr. Michel Jeanjean from the Catholic University of Louvain (UcL) as principal investigator. The province of Luxembourg, the biggest Belgian province, is a largely rural region with a total resident population of only 270,000 inhabitants. Yearly migration flows with the other Belgian provinces are rather small, with more or less 4,000 out-migrants and 5,000 in-migrants (data for the year 2006). When the register was set up, its cardiovascular death rate was rather high compared to that of the other Belgian
provinces. Presently, life expectancy in Luxembourg is still lower than the Belgian average, especially for males.

The reference population of the register is composed of the individuals aged 35 to 74, who are Belgian and residing in the Province of Luxembourg. The register is run by the « Association Interuniversitaire pour la Prévention des Maladies Cardiovasculaires », composed of experts of different disciplines (cardiology, diabetology, biology, demography,…) coming from the main francophone universities in Belgium (Universities at Louvain-la-Neuve, Liège, Brussels, and the Mont-Godinne university hospital).

BELLUX registers not only myocardial infarcts and coronary deaths, as specified by the MONICA protocol, but also since 1985 all coronary invasive diagnostic and therapeutic interventions: coronary arteriography, PCI¹, CABG², revascularization procedures. The reason for incorporating these invasive diagnostic and therapeutic procedures performed on the target population is that acute myocardial infarctions do not represent all the cases of coronary heart diseases. It is therefore important to determine the angiographic appearance of coronary vessels. Registering both infarcts and interventions thus leads to a better estimation of the degree of atheromatosis and coronary heart disease in the population. On the other hand, stroke was not recorded by BELLUX for the reasons given in section 2. Actually, in the period 1985-90, many strokes were treated at home and it was hardly possible to obtain the information from the GPs.

Registration of coronary events is based on the following procedure. For fatal cases, information is obtained from the cause of death specified on the death certificate, for deaths occurring to residents of the Province, and validated by hospital records. The information for sudden deaths is less reliable, as autopsies are rarely performed. For non-fatal cases, sources of data are exclusively hospital records with diagnosis of discharge (the so-called cold pursuit method); practically no infarcts are treated solely at home. Potential candidates are detected from entry registers at emergency wards and from hospital records (the résumé clinique minimal - RCM - or minimum clinical data at discharge). As non-fatal cases can also be detected outside the Province, the geographic coverage of sources extends to hospitals outside the Province, the latter hospitals informing the local hospital in the Province from which the

¹ Percutaneous Coronary Intervention
² Coronary Artery Bypass Graft
patient was sent. Concerning invasive diagnostic and therapeutic procedures, the data come from the same sources, *i.e.* the RCMs; once again, hospitals outside the Province are also taken into account.

In addition to the registration of coronary events, BELLUX has also conducted in 1983 a sole baseline random population survey in the Province, in order to collect data on a wide series of health factors, personality type (Jenkins questionnaire), nutrition, smoking, lifestyle, and socio-economic characteristics. Around 2,000 persons, both males and females, were interviewed, aged 20 to 50. For those who accepted, the interview was followed by a free medical examination. Various results on risk factors are presented in Brohet *et al.* (1988).

### 3.2 Some results from the MONICA-BELLUX Register

The following figure 2 presents both for males and for females the trends in the incidence of coronary events (both infarcts and interventions) from 1985 to 2004, for the population aged 35 to 74 in the Province of Luxembourg, as registered by BELLUX.

*Figure 2. Trends in the incidence of coronary events (infarcts and interventions)*

1985 to 2004, ages 35 to 74 (*MONICA-BELLUX register*)

As one can see, the incidence has remained rather stable during the past years. This is however due to compensating trends in the number of infarcts and interventions (figure 3): the former are on the decline, while diagnostic and therapeutic invasive procedures considerably increased over the years (see Schroeder *et al.*, 2008).

*Figure 3. Trends in infarcts and interventions* (*MONICA-BELLUX register*)

In the Province of Luxembourg, both the incidence and incidence rates of myocardial infarction for both sexes are on the decline since 1985, as is also observed in a number of other countries (Tunstall-Pedoe *et al.*, 1999), thanks to a decrease in risk factors such as cholesterol levels, smoking, or diastolic blood pressure. The following figure 4 presents the age-standardized incidence rates for males aged 35-74 (per 100,000 inhabitants) obtained from the BELLUX data, for the period 1985-2005 (Schroeder, 2009).
This favourable trend is however not seen for the case fatality rates, which have unfortunately remained stable over the years. The following figure 5 shows the trends in case fatality rates for males, for the age groups 35-54, 55-64, and 65-74. The trend is stable over time whatever the age group.

More generally, in the MONICA populations in which mortality decreased, coronary event rates contributed two thirds and case fatality one third on average (Tunstall-Pedoe et al., 1999). Furthermore, for men there was no significant correlation between coronary event and case fatality rates. For women, there was on the contrary an inverse correlation between event and case fatality rates.

5. Discussion and conclusions

A major difficulty of long term projects such as the MONICA one is to sustain the project over the years. Some centres have stopped registering data altogether, e.g. MCC 25 Heidelberg after retirement of the principal investigator, and others, such as MONICA-BELLUX, collaborated for many years but were unable to wholly satisfy the MONICA protocol requirements and were not included in the final set of collaborating centres. The reasons for this are multiple. According to Tunstall-Pedoe (ed.) (2003, p. 127), some centres failed to meet deadlines for data, some discovered major problems with their data which could not be resolved, others failed to obtain continuous funding for the local activities, and some simply lost contact failing to reply to repeated communications.

Concerning CVD registration more specifically, several issues can be raised (Tunstall-Pedoe et al., 1994; Gourbin, 1997; Tunstall-Pedoe P. (ed.), 2003). First, as CVD registers do not

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3 As stated previously, BELLUX could only complete one sole population survey, due to lack of funding.
cover a whole country, events can occur outside the population of reference, in our case outside the Province of Luxembourg. For example, a patient resident in the Province of Luxembourg might be hospitalized in the Province of Liège. Access to hospital discharges outside the area of reference is therefore required. Secondly, the same event can be declared by multiple sources, *e.g.* a hospital and a general practitioner. It is thus necessary to link all events to the same individual by *e.g.* his/her personal identification number. Of course, one also has to have access to the cause of death declared on the death certificates, irrespective of possible privacy issues. Then there is the problem of diagnosis: diagnoses on hospital discharges or on death certificates do not necessarily correspond to the strict MONICA criteria for definite myocardial infarction and must be checked if possible. The MONICA project showed that a large proportion of deaths had no relevant clinical or autopsy information. The disagreement between hospital diagnoses and the MONICA criteria is especially problematic in the *cold pursuit* procedure that has been used by many centres. In this approach, potential cases for registration are identified through the more or less reliable diagnoses on listings of hospital discharge records, often leading to fewer cases than in the *hot pursuit* of admissions approach where the patient is still in care and complementary information can be obtained by the Centre’s team. On the other hand, cold pursuit is cheaper and easier to carry out than its hot version. Finally, CVD registers cannot identify missed or misdiagnosed coronary events. And potential patients may not seek medical care and in this case are not investigated.

Notwithstanding these issues, CVD registers remain an invaluable source of data for monitoring levels and trends in incidence and case fatality. Recent methods of diagnosis both for coronary events and stroke now lead to much more trustworthy results than a few decades ago. Though the incidence rate is declining in western countries, the prevalence of CVD will nevertheless remain high for the years to come due to the ageing of the population, CVD being mainly diseases of older ages. Due to the increase in life expectancy at older ages, the 64-year upper limit initially recommended by MONICA for registering myocardial infarctions is presently too low, and various registers such as BELLUX have extended the age limit to 74 or more. We can recommend opting for these higher ages, possibly pushing the upper age limit to 84 as the BELLUX register has recently done. Above 85, it however becomes difficult to disentangle the multiple pathologies often present in very old individuals.
The BELLUX data, among others, have shown that trends in incidence rates, on the one hand, and in case fatality rates, on the other hand, can significantly differ from one another. In the Province of Luxembourg, case fatality rates have even remained stable over time, while incidence rates have declined. This situation requires better detection of individuals at risk. The intervention component of the BELLUX register is well-suited for this task, as it enables detecting the presence and extent of atheromatosis, a factor which might lead to a coronary event.

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Figure 1. Age-standardized coronary event incidence rates (ages 35-64): final three years of registration

Source: Luepker (2011)
Figure 2. Trends in the incidence of coronary events (infarcts and interventions) 1985 to 2004, ages 35 to 74, (MONICA-BELLUX register)
Figure 3. Trends in infarcts and interventions (MONICA-BELLUX register)
Figure 4  Trends in myocardial infarction incidence rates (MONICA-BELLUX register)
(Age-standardized rates for males, ages 35-74)
Figure 5. Trends in case fatality rates, males, ages 35-54, 55-64, 65-74

(MONICA-BELLUX register)