

The Manresa study: a stimulus for the development of cardiovascular epidemiology in Spain

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Of the different types of observational studies available in epidemiology, longitudinal studies are generally considered to provide the most valuable information regarding the association between exposure and disease. These cohort studies can be used to estimate risks, and rates or time of occurrence of events of interest.¹ One of the many advantages of longitudinal studies is the ability to describe the natural history of a disease from the time of exposure and to calculate its incidence. Nevertheless, longitudinal studies are not exempt from inconveniences, especially when they are undertaken in the general population. These inconveniences include their lack of efficiency in the case of rare diseases, important logistic problems related with the usually prolonged duration of the study, difficulties in follow-up and the high cost.

Cohort studies involving groups of workers are a special case. This situation reduces some of the long-term inconveniences of longitudinal studies undertaken in the general population of a community. Studies in a working population often enable a historical cohort design to be used. Members of this type of cohort can be identified now and when they entered the study. The cohort, once identified, is then observed up to the present time or up to a particular date and all events of interest during this observation period can be registered. This identification requires the presence of baseline information and a clear date of inclusion in the cohort. A typical example is the first medical examination given to workers when they start to work in a company. The net effect of this design is that not so many years of observation are required from the time the study hypothesis is suggested, as there is a part of the cohort with a "historical follow-up." The advantage of this is obvious, but unfortunately it is not always applicable to any hypothesis, because the required information must be available in registries and, when undertaken in a working population, certain problems arise concerning the general applicability of the results. These problems derive from the fact that workers, simply because they are workers and especially in certain particular jobs, are healthier than the general population to which they belong. The argument is that in order to be a worker you have to be healthy. This implies some degree of selection when starting work, which qualifies the workers for inclusion in the study. Occasionally, for certain hypotheses, this qualification is of little importance but in other cases it may assume a greater importance. Thus, estimates of the frequency of a disease are generally lower than in the general population.

Sometimes it is logistic reasons, such as those mentioned, or other reasons which encourage the use of observational studies in working populations. At other times, this type of study is the most obvious alternative when the hypothesis refers to an association between exposure to certain factors in the working environment and the risk of becoming ill. This is the case with exposure in the rubber industry, which has been associated with an increased risk of a wide variety of diseases, including different cancers (bladder cancer, lung cancer, leukemia, etc), ischemic heart disease, hypertension, and a worsened intellectual and psychomotor function.²

The article by Puig et al³ in this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA analyzes mortality in a cohort of workers involved in the rubber industry. To this extent, the study resembles those mentioned previously. Importantly, the study found that the main causes of death, cancer and cardiovascular disease, were similar to those of the general male population in Catalonia and to those in the whole of Spain. More specifically, the main causes of death were lung cancer and acute myocardial infarction. Moreover, no excess mortality was detected in this cohort related with environmental exposure. In fact, this cohort of male workers had a lower mortality than that of the general population of a similar age and sex from which they came. The authors of the study attribute this lower mortality to the "healthy worker effect", mentioned above. Nevertheless, the authors are cautious, and because of the size of the cohort (several times smaller than other similar cohorts in the industrial sector), no mention is made of risk reduction in specific disease groups (cancer and cardiovascular disease). However, no serious problem with the power of the study seems to justify this because, except for certain specific

causes in the oldest group of participants, the trend was always the same: fewer deaths than expected. Even the evolution of mortality over time was similar to the pattern seen in southern Europe.

What, then, makes this study special and, in the opinion of the editors, worthy of an editorial comment? One should, perhaps, ask the editors, but I believe there are several reasons. Firstly, the aim, origin and later development of the study providing the data mean that it resembles more closely other studies rather than those which just search for the effect of exposure in the working environment on the risk of becoming ill. The study in question made good use of the working environment to examine with a certain guarantee the enormous difficulties involved in answering important questions in the area of cardiovascular epidemiology. The design and performance of the study make it directly comparable with some of the most important studies undertaken in this field. Notable examples of longitudinal, observational cardiovascular studies undertaken in the working environment include the studies of the Western Electric Company and the Peoples Gas Company, both in Chicago and started in the mid or late 1950s and which are still providing valuable information,⁴ the Western Collaborative Group Study in California or the Dupont Company study. In Europe, we have the Whitehall study of London civil servants, started at the end of the 1960s.⁵ The working environment has been used successfully not only for undertaking observational studies, but also for clinical trials of prevention of cardiovascular disease.⁶

As recently mentioned by one of the researchers who started it, the Manresa study began in April 1968.⁷ The study shares many of the virtues of the studies mentioned above, and some of their limitations. Foremost among the virtues are the foresight shown by the researchers to start the study when they did. Even though the Framingham study was already some 20 years old at the time and the first studies in companies some 10-15 years old, ischemic heart disease was not the main health care concern of Spanish cardiologists at that time; and even less so study of its risk factors! Initiation of this type of study at that particular moment has enabled such a long observation of this cohort, which was, moreover, almost "virgin" at its outset as far as treatment of risk factors was concerned. This would be impossible nowadays. The study, like all similar studies, is a result of its time and setting. Thus, in common with most of those studies on which it was doubtless based, the study was undertaken in a group of middle-aged men. This was partly because it was easier to find working men of this age, but importantly, it was also because this age group was thought to be a group with a high incidence of coronary heart disease in whom preventive measures would have the greatest benefit. General interest in coronary heart disease and its risk factors in other groups of persons, such as women or older persons, came later.

From the start of the Manresa study in 1968, follow-up studies were undertaken every five years or so up to 1996. The article published in this issue of the *REVISTA ESPAÑOLA DE CARDIOLOGÍA* provides information on mortality up to 1996. Many things happened over these 28 years, including the fact that one out of 4 workers who were healthy at the start of the study died. The long observation period also enabled stable mortality rates to be calculated. A few years ago one of the researchers who had spent almost all career involved in the Framingham study commented, informally and jokingly, that the study had, to a certain extent and from his point of view, become a sort of competition to see who lived longer, the initial cohort or the researchers. I should add that he was happy to be winning! This sort of dedication to work has resulted in much better understanding of the determining factors of coronary heart disease in Spain and in the rest of the world.

By this stage of the editorial, I hope I have made quite clear my respect and appreciation for those who started this pioneering study in Spain and who have kept it going until now. Just as those other studies in the United States and Europe have been the foundation for the development of cardiovascular epidemiology throughout the world, the Manresa study has achieved the same purpose in Spain. This is so not only because of the study's unique scientific results,⁸ coming as they do from our own environment and dating back to the start of the study, but also because they will hopefully continue to enrich our future and, more especially, open the door to further developments in this scenario in Spain. The Manresa study has shown us that this type of study is feasible, even in unfavorable settings and with limited resources. Added to which, a by-product of the study was the first and still, I believe, the only 10-day teaching seminar of cardiovascular epidemiology undertaken in Spanish. Contacts with colleagues in other countries and the encouragement of the main researchers in the Manresa study were key to the organization in 1985, at El Paular, Rascafría, near Madrid, of the Seminar of the World Heart Foundation Council of Cardiovascular Epidemiology. This seminar, at which several of the main researchers of the studies mentioned above were present, including those of the Manresa study, was a stimulus and an opportunity from which many of us involved in cardiovascular epidemiology have tried to benefit, to a greater or lesser extent. I therefore congratulate the researchers of the Manresa study for their work over all these years and encourage them to carry on.

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