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Non-participants differ from participants as regards risk factors for vertebral deformities

A source of misinterpretation in the European Vertebral Osteoporosis Study

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ABSTRACT – Interpretation of data in epidemiological cohort studies may be confounded if differences exist between non-participants and participants. In the Malmö part of the European Vertebral Osteoporosis Study (EVOS), which was designed to evaluate the prevalence of vertebral deformity in 50–80-year-old persons, we compared 74 men and 95 women who had been invited, but declined to participate with age- and gender-matched participants as regards alcohol abuse, previous fractures and subsequent mortality, factors known to affect the prevalence of vertebral deformity.

We found more men with alcohol abuse, more men with a previous fragility fracture and a tendency to more men with a previous clinical vertebral fracture among the non-participants than in the male participants. In contrast, there were fewer female non-participants than female participants with a previous clinical vertebral fracture. The mortality rate during the decade after the baseline examination was higher among both male and female non-participants.

The “true” prevalence of vertebral deformity in the whole male population at risk in Malmö seems to be underestimated in the EVOS study. In women, it is more difficult to estimate the combined result of the confounding factors. Conclusions based on the EVOS participants may not be applicable to the whole population at risk.

However, interpretation of data may be confounded if baseline discrepancies exist between non-participants and participants as regards factors known to affect the endpoint. If the participation rate is low, any differences in similar confounding factors may lead to erroneous inferences if we extrapolate our conclusions from the sample measured to the whole population at risk.

The European Vertebral Osteoporosis Study (EVOS) included men and women aged 50–80 years from 36 centers in 19 European countries. Its aim was to study the epidemiology of vertebral deformity in the thoracic and lumbar spine (O’Neill et al. 1996). O’Neill et al. (1995) evaluated various lifestyle factors known to affect the rate of vertebral deformity in several participating subgroups in the EVOS cohort. They found only small differences between the sub-groups of no relevance to an increase or decrease in the risk of vertebral deformity.

We evaluated alcohol abuse, the incidence of fractures and the mortality rate in invited non-participants and matched participants in the Malmö part of the EVOS cohort, factors known to affect the prevalence of vertebral deformity (Israel et al. 1980, Seeman et al. 1983, Ross et al. 1991, Cooper et al. 1993, Peris et al. 1995, Ismail et al. 1998, Kado et al. 1999, Klotzbuecher et al. 2000).

We hypothesized that the invited non-participants were a less healthy subgroup with a higher prevalence of vertebral deformity than the participants. This would suggest that the conclusion

Population-based studies are usually regarded as the “golden standard” when evaluating epi-

drawn from the sample should not be extrapolated to the whole population of Malmö. We wished to know whether the non-responders (i) have had more previous fractures than the responders, (ii) include more persons with alcohol abuse than the responders, and /or (iii) have a higher mortality rate than them.

Subjects and methods

The EVOS is a multi-center study designed to evaluate the prevalence of vertebral deformity on lateral radiographs of the thoracic and lumbar spine. Baseline measurements were made on 50–80-year-old men and women from 36 centers in 19 European countries in 1990–1991 (O'Neill et al. 1996). The Malmö part of the EVOS was a population-based cohort study with persons randomly selected from the city files. The aim was to recruit 300 men and 300 women. Of the 600 subjects initially invited, 129 declined to participate. These were replaced by their register neighbours from the city files. Altogether 767 persons were finally invited and 598 (78%) took part in the study. 74 men with a mean age of 66 (50–80) years and 95 women having a mean age of 67 (50–80) years declined to participate. In this study, each non-participant was compared to two age- and gender-matched participants as regards differences in alcohol abuse, fracture rate and subsequent mortality.

As all radiographs, referrals and reports have been saved in the archives of Malmö University Hospital (UMAS) since the beginning of the last century, we could identify persons with alcohol abuse and/or a history of fractures. UMAS is the only emergency hospital in Malmö, a Swedish city of nearly 250,000 inhabitants. Virtually all patients who need medical care for more severe alcohol problems or a fracture are seen at UMAS. Fractures sustained by this population, but outside the city, are usually referred to the Department of Orthopaedics and the Department of Diagnostic Radiology for follow-up, at which time they are classified to ensure a correct diagnosis. Less than 3% of all patients with a fracture in the city are seen by a private physician during treatment, usually minor fractures in no need of treatment (Jóns-

son 1993). Such fractures are not classified in the hospital archives.

In this study, the number of persons with a fracture and the total number of fractures were registered. Fractures were classified as (i) clinical vertebral fractures (diagnosed by a radiologist), (ii) fragility fractures (upper end of the humerus, distal end of the forearm, trochanteric and cervical hip, tibial condyle, ankle and pelvic rami fractures), and (iii) other fractures (skull, face, ribs, digits, metatarsals, metacarpals, diaphyseal). Fracture events until the study's start were registered.

Data from the Department of Alcohol Diseases (DAD) at UMAS were evaluated to define alcohol abuse. Registration in the DAD was used as the criterion for alcohol abuse in the present study. Most of the registered persons had voluntarily sought medical advice at the DAD, but some had also been admitted at the time of severe bouts. Alcohol abuse until the study started was registered.

The mortality rate of the non-participants and the participants was recorded by use of the Swedish Population Records from the start of the study until February 2000.

Data are presented as the number of persons or number of fractures in each group. The findings in non-participants and participants were compared with the chi square test, with $p < 0.05$ regarded as a statistically significant difference.

The study was approved by the Ethics Committee at the University of Lund, Sweden.

Results

Men

We found that more male non-participants than male participants had alcohol abuse ($p = 0.02$), a previous fragility fracture ($p = 0.05$) and a previous clinical vertebral fracture ($p = 0.08$) (Table). The mortality rate during the decade after the baseline examination was also higher in the male non-participants than the male participants ($p = 0.003$).

Women

In contrast, fewer female non-participants than female participants had had a previous clinical vertebral fracture ($p = 0.05$) (Table). The mortality rate during the decade after the baseline examina-

Number of persons with alcohol abuse, with a clinical fracture, number of fractures sustained before baseline and mortality rate during the decade after the baseline measurement in the 169 persons in Malmö who were invited but refused to participate in the European Vertebral Osteoporosis Study (EVOS) compared with 338 age- and gender-matched persons in Malmö who participated in the study

	Men			Women		
	Non-participants (n=74)	P-value	Participants (n=148)	Non-participants (n=95)	P-value	Participants (n=190)
Number with alcohol abuse	10	0.02	7	1	1.00	2
Number with fractures						
any fracture	22	0.28	34	36	0.70	76
any fragility fracture	9	0.05	7	23	0.30	58
vertebral fractures	4	0.08	2	2	0.05	15
Number of fractures						
vertebral fractures	4	–	2	2	–	8
fragility fractures	13	–	7	27	–	69
other fractures	26	–	34	21	–	46
All fractures	43	–	43	50	–	133
Number of deaths	34	0.003	38	30	0.007	33

tion was higher in the female non-participants than the female participants (p = 0.007)

Discussion

Jónsson et al. (1992) and Jónsson (1993) reported, when evaluating bone mass, fractures and lifestyle factors, that the non-participants had a higher incidence of previous fractures and were more frequently registered as patients in the Department of Alcoholic Diseases (DAD) than the participants. Other prospective cohort studies report more alcohol problems in male non-participants than in male participants (Wilhelmsen et al. 1976, Janzon et al. 1986). It seems probable that the greater alcohol abuse among the male non-participants is responsible for a lower bone mass and more traumas in this sub-cohort, probably explaining the higher incidence of vertebral fracture among the male non-participants than in the male participants (Israel et al. 1980, Seeman et al. 1983, Peris et al. 1995). In contrast, women with a previous vertebral fracture seem to be more interested in participating in a cohort study like the EVOS. Unlike the men, we found no difference in alcohol abuse between the female non-responders and the female responders, but as only 3 women were classified as having alcohol abuse, there is a risk of a type II error. Our findings do not accord with those of Jónsson et al. (1992) who reported that more female non-par-

ticipants were registered at the DAD than female participants in a previous larger study cohort.

Male and female non-participants also had a higher mortality rate than male and female participants which supports the data of two cohort studies—i.e., one preventive trial against coronary heart disease in middle-aged men and one prospective study of general health in 66-year-old men and women (Wilhelmsen et al. 1976, Enzell 1984). It seems that non-participants usually have poorer health and a higher risk of an associated vertebral deformity than participants (Ross et al. 1991, Ettinger et al. 1992, Matthis et al. 1998).

How do the data in our present study affect the conclusions of the original EVOS study? The latter study evaluated the prevalence of vertebral deformity in men and women between 50 and 80 years of age. As the male non-participants included more persons with a previous fracture, more alcohol abusers and those with a higher subsequent mortality rate, all risk factors for vertebral deformity, the “true” prevalence of vertebral deformity would be higher if all invited male subjects had participated. That is, the “true” prevalence of vertebral deformity in the whole male population in Malmö was underestimated in the male EVOS participants.

On the other hand, it is more difficult to estimate the “true” prevalence of vertebral deformity in the total female population at risk in Malmö. The lower incidence of previous clinical vertebral fractures in the female non-participants indicates that

the female participants are more prone to sustain a vertebral deformity than the female non-participants. In contrast, the higher mortality rate of the female non-participants indicates that the participants are a healthier subgroup, and have fewer vertebral deformities than the non-participants, who have poorer health and more vertebral deformities than a healthier population (Ross et al. 1991, Ettinger et al. 1992, Matthis et al. 1998).

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