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Diabetes mellitus, impaired glucose tolerance and mortality among elderly men: The Finnish cohorts of The Seven Countries Study

J. H. Stengård[1], J. Tuomilehto[1], J. Pekkanen[1], P. Kivinen[2], E. Kaarsalo[3], A. Nissinen[2] and M. J. Karvonen[4]

[1] National Public Health Institute, Department of Epidemiology, Helsinki
[2] Department of Community Medicine and General Practice, University of Kuopio, Kuopio
[3] Loimaa District Hospital, Loimaa, Finland [4] Pioppi, Italy

Summary. We studied the association of glucose intolerance with total and cause-specific mortality during a 5-year follow-up of 637 elderly Finnish men aged 65 to 84 years. Total mortality was 276 per 1000 for men aged 65 to 74 years and 537 per 1000 for men aged 75 to 84 years. Five-year total mortality adjusted for age was 364 per 1000 in diabetic men, 234 per 1000 in men with impaired glucose tolerance and 209 per 1000 in men with normal glucose tolerance. The relative risk of death among diabetic men was 2.10 (95 % confidence interval 1.26 to 3.49) and among men with impaired glucose tolerance 1.17 (95% confidence interval 0.71 to 1.94) times higher compared with men with normal glucose tolerance. Cardiovascular disease was the most common cause of death in every glucose tolerance group. The multivariate adjusted relative risk of cardiovascular death was increased (1.55) in diabetic patients, albeit non-significantly (95 % confidence interval 0.84 to 2.85). Diabetes resulted in an increased risk of cardiovascular mortality among men aged 65–74 years but not among the 75- 84-year-old men. Relative risk of death from non-cardiovascular causes was slightly increased among diabetic subjects. In conclusion, diabetes mellitus is a significant determinant of mortality among elderly Finnish men.

Key words: Diabetes mellitus, elderly, mortality, cardiovascular disease.

People with diabetes mellitus have an increased risk for dying prematurely [1–4]. This risk varies considerably however, between different populations [5] and between different age groups within a population [4]. In middle-aged diabetic subjects relative risk of death has been found to range from two to four, compared to non-diabetic subjects [1–4]. In elderly diabetic patients the reported relative risk has usually been below two [2, 4, 6–8]. In diabetic patients aged 75 years and over, excess mortality has disappeared in some [2, 6], but not all [9, 10] studies. Few studies of mortality among elderly diabetic subjects have been made and more information is needed to assess the impact of diabetes on the prognosis of these patients [4]. Accordingly, few data exist concerning mortality among elderly subjects with impaired glucose tolerance.

Cardiovascular disease is the major cause of excess mortality in diabetic patients, particularly in western countries where atherosclerosis is a very common complication of diabetes [2, 4, 5, 8, 10–14]. Accelerated development of atherosclerosis in diabetes is associated with adverse levels and composition of plasma lipids and lipoproteins and increased occurrence of hypertension in diabetic patients [13, 15, 16]. Most of these abnormalities also occur in subjects with impaired glucose tolerance [16]. The excess risk of death from cardiovascular disease in diabetic patients cannot, however, be completely explained by an unfavourable risk factor profile and diabetes per se also is considered to be an independent risk factor [13]. The present paper examines the association of diabetes and impaired glucose tolerance with cause-specific and all-cause mortality during a 5-year follow-up of 637 Finnish men aged 65 to 84 years, the Finnish cohorts of The Seven Countries Study.

Subjects, materials and methods

The Seven Countries Study was started in the late 1950's to study cardiovascular disease mortality and morbidity and risk factor levels in different countries, including Finland [17]. The original Finnish cohorts consisted of all men born between 1900 and 1919 in two geographically defined rural areas, one in eastern and the other in south-western Finland, totalling 1711 men. At the time of the 25-year follow-up survey in 1984, men were 65–84 years old and 766 men were still alive. Of these men 716 (93 %) at least participated in the medical examination.

In 1984, all men were requested to fast for at least 4 h before the examination (mean fasting time 13 h, SD 5 h). At the clinic blood samples were drawn from an ante-cubital vein for laboratory analysis of total and HDL cholesterol levels. Body weight was measured

Table 1. Mean age of the men and age-adjusted baseline characteristics in 1984 by glucose tolerance status.

Variable	Glucose tolerance status in 1984					
	Normal ($n=216$)		Impaired ($n=234$)		Diabetes mellitus ($n=187$)	
Age[a]						
Mean (SD)	71.4	(4.8)	72.5	(5.2)	73.3	(5.2)
Anthropometry						
Body mass index Mean (SD)	25.5	(3.9)	25.9	(4.0)	26.0	(4.2)
Obese[c] (%)	34.2		40.7		40.6	
Blood pressure						
Systolic[a] (mm Hg) Mean (SD)	151	(22)	156	(22)	157	(24)
Diastolic (mm Hg) Mean (SD)	87	(11)	88	(11)	87	(11)
Hypertensive[a, d] (%)	56.8		60.2		65.8	
Serum cholesterol						
Total[a] (mmol/l) Mean (SD)	6.2	(1.1)	6.3	(1.3)	6.0	(1.3)
HDL[a] (mmol/l) Mean (SD)	1.3	(0.3)	1.2	(0.3)	1.2	(0.3)
Smoking habits[b]						
Current smokers (%)	27.8		19.2		13.4	
Ex-smokers (%)	50.9		54.4		61.3	
Functional capacity						
Mean of sum score (SD)[a, e]	47.9	(6.2)	47.9	(6.8)	45.8	(7.8)

[a] Differences between glucose tolerance groups significant at $p<0.05$
[b] Difference between groups significant at $p<0.01$
[c] Subject was defined as obese, if body mass index was 27 kg/m^2 or more
[d] Definition of hypertension according to the recommendation of World Health Organization (25)
[e] High sum score indicates good functional capacity

in light clothing and recorded to the nearest 100 g. Blood pressure was measured twice on the right arm by a specially trained nurse after 5 min rest with subjects in the supine position. The mean value of the two measurements was used in the analyses. Smoking status was assessed using a standard questionnaire [18]. Subjects were divided into the following three categories: never smokers, ex-smokers and current smokers. Those who had stopped smoking less than 1 year before the examination were considered as current smokers. Functional capacity of the men was assessed by using a sum index of 13 questions about self-care and daily living activities. The men were asked whether they are able to move outdoors, to walk at least 400 m, to wash and bath themselves, or perform light or heavy house work or both, for instance [19]. The detailed study protocol of the 1984 survey has been described elsewhere [20].

Total and HDL cholesterol concentrations were analysed using an enzymatic method (Monotest, new; Boehringer Mannheim, GmbH, Mannheim, FRG) and Olli C 3000 photometer (Kone, Oy, Finland). Total cholesterol was determined from fresh serum samples [21]. HDL cholesterol was measured after precipitation of VLDL and LDL with dextran-magnesium-chloride [21].

Glucose tolerance was tested by using a 75 g oral glucose load. Blood glucose levels were measured at fasting and 2 h after a glucose load from capillary blood using a refractometric method (Glucometer refractometer; Miles Laboratories, Ames Division, Elkhart, Ind. USA). The test took place between 08.00 and 16.30 hours [22].

The men were classified hierarchically according to the current criteria of World Health Organization for diabetes and impaired glucose tolerance [23]. Subjects whose post-load blood glucose was 11.1 mmol/l or more were considered as diabetic. Impaired glucose tolerance was defined as 2 h post-load blood glucose between 7.8 mmol/l and 11.1 mmol/l. Men who were treated with insulin or oral anti-diabetic drugs, or whose fasting blood glucose was over 10.0 mmol/l were excluded from the glucose tolerance test and directly classified as having diabetes. Altogether 637 men could be successfully classified according to these criteria. Of these, 187 had diabetes, 234 impaired glucose tolerance and 216 normal glucose tolerance. Nine of the diabetic subjects received insulin and 36 were on oral anti-diabetic drugs. Seventy-nine men could not be classified because 49 participated only in the assessment of fasting blood glucose, and 30 underwent no blood glucose determinations at all. Most of these unclassified subjects were hospitalized or they were examined at home.

There were 50 non-participants in 1984. Reasons for non-participation included long travel distance, recent myocardial infarction, severe rheumatic arthritis and refusal to participate. Of these 50 non-participating and 79 participating men whose glucose tolerance remained unclassified, a total of 71 (55 %) men died between 1984 and 1989.

At the time of 30-year follow-up in 1989, 524 men were still alive and 242 had died between 1984 and 1989. The vital status of 513 men was ascertained through personal contacts and 11 through the Finnish Population Registry. Death certificates and hospital records were obtained for all the deceased men and coded by one of the authors (J. P.) according to fixed priority rules [18].

Statistical analysis

The statistical analyses were performed with SAS statistical software [24]. Differences between distinct glucose tolerance groups in continuous variables were tested using analysis of variance and for categorical variables using Cochran-Mantel-Haenzel test. Odds ratios were estimated using multiple logistic regression analysis. Multivariate analysis always included age, body mass index, hypertension, smoking history, total and HDL cholesterol and sum index of functional capacity. Hypertension was defined according to recommendations of the World Health Organization (systolic blood pressure 160 mm Hg or more or diastolic blood pressure 95 mm Hg or more or both, or current antihypertensive drug treatment) [25]. Since there were no significant interactions between area of residence and glucose tolerance group in any of the mortality analyses, all the results are presented together for eastern and south-western Finland.

Results

Baseline characteristics of the subjects are presented in Table 1. Both diabetic men and subjects with impaired glucose tolerance were older than those with normal glucose tolerance. Of the known cardiovascular risk factors, both the mean value of systolic blood pressure and occurrence of hypertension were higher in men with diabetes or impaired glucose tolerance, and serum HDL cholesterol level was lower compared to subjects with normal glucose tolerance. The mean level of diastolic blood pressure was similar among the three glucose tolerance groups. Similarly, neither the mean body mass index nor the prevalence of obesity in subjects with diabetes or impaired glucose tolerance differed from that found in men with normal glucose tolerance. The proportion of current smokers was lower and ex-smokers higher in diabetic patients and in subjects with impaired glucose tolerance compared to subjects with normal glucose tolerance. The mean level of

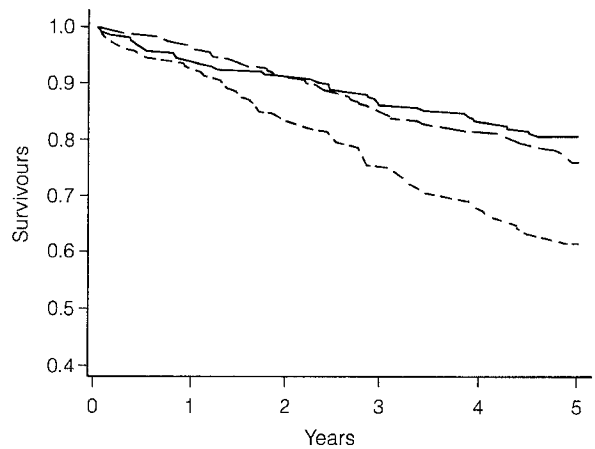

Fig. 1. Crude Kaplan-Meier survival probabilities over 5-year follow-up for subjects with diabetes mellitus (----), impaired glucose tolerance (– –)or normal glucose tolerance (—)

serum total cholesterol and the degree of functional capacity were lower in diabetic men than in the others.

During the 5-year follow-up, a total of 171 deaths were recorded among men whose glucose tolerance status was determined at baseline. Of these, 73 had been diabetic, 56 had impaired glucose tolerance and 42 normal glucose tolerance. Comparison of the 5-year survival probability curve for diabetic men with those for impaired or normal glucose tolerance shows the highest mortality for diabetic patients (Fig. 1). Age-adjusted total mortality in the diabetic group was 364 per 1000 men (Table 2). Relative risk of death in diabetic men was two times greater than that found in subjects with normal glucose tolerance after adjusting for age, body mass index, smoking history, serum total and HDL cholesterol, hypertension, and functional capacity (Table 3). Among diabetic patients age-specific total mortality was 276 per 1000 men for those aged 65 to 74 years and 537 per 1000 men for those aged 75 to 84 years (Table 4). The relative risk of dying in the younger diabetic group was twice that obtained for subjects of the respective age group with normal glucose tolerance. In the older diabetic group the mortality risk was not changed significantly.

The risk of dying was the highest in diabetic patients treated with anti-diabetic drugs (Tables 2 and 3), particularly if insulin was used. Multivariate-adjusted relative risk for diabetic subjects treated with oral agents was 2.82 (95% confidence interval (CI) 1.22 to 17.09) and in insulin-treated patients 9.56 (95% CI 1.58 to 57.88) compared with subjects with normal glucose tolerance. There were, however, only nine insulin-treated subjects and seven deaths among them.

In subjects with impaired glucose tolerance both all-cause and cause-specific mortality was between that of diabetic and non-diabetic patients, but the change was not statistically significant compared with non-diabetic men (Tables 2 and 3).

Cardiovascular disease was the most common cause of death in every glucose tolerance group. During the follow-up a total of 91 cardiovascular deaths were recorded, of which 36 occurred among diabetic subjects. Age-adjusted cardiovascular disease mortality in the diabetic group was 184 per 1000 men (Table 2). After adjustment for age and several major risk factors for chronic diseases the risk estimate for cardiovascular death in the diabetes group varied within the same range that was obtained for subjects with impaired or normal glucose tolerance (Tables 2 and 3). Among diabetic patients age-specific cardiovascular disease mortality was 152 per 1000 men in those aged 65 to 74 years and 244 per 1000 men in those aged 75 to 84 years (Table 4). Relative risk for cardiovascular death was significantly increased in the younger diabetic group but not in the older one. In insulin-treated diabetic patients the relative risk was 4.19 (95% CI 0.92 to 18.92).

Cancer was the most common non-cardiovascular cause of death. During the follow-up 42 men died from cancer, of whom 19 had diabetes. Multivariate-adjusted relative risk for death from cancer was not significantly different among the three glucose tolerance groups although the diabetic patients tended to have a higher risk (Tables 2 and 3).

The age-adjusted rate for non-cardiovascular/non-cancer cause of death varied from 2.8% in subjects with normal glucose tolerance to 8.6% in diabetic men (Table 2). Multivariate-adjusted relative risk of non-cardiovascular/non-cancer death in diabetic patients was statistically significant only among those treated with hypoglycaemic agents (Table 3). Of the 38 deaths that were due to reasons other than cardiovascular disease or cancer, 19 were due to infection. Of these, eight occurred among diabetic patients and nine among subjects with impaired glucose tolerance, and only two in men with normal glucose tolerance (Table 5).

Table 2. Age-adjusted 5-year mortality rates by glucose tolerance status in 1984

Glucose tolerance status		Cardiovascular deaths		Cancer deaths		Other deaths		All deaths	
	Number of men	Number of deaths	Rate per 1000 men	Number of deaths	Rate per 1000 men	Number of deaths	Rate per 1000 men	Number of deaths	Rate per 1000 men
Normal	216	23	118	13	62	6	28	42	209
Impaired	234	32	134	10	43	14	58	56	234
Diabetes	187	36	184	19	94	18	86	73	364
Diabetes by treatment									
– diet alone or none[a]	142	24	169	13	92	10	70	47	331
– hypoglycaemic agents	45	12	267	6	133	8	178	26	578

[a] Includes both newly-diagnosed diabetic patients and known diabetic patients treated with diet alone

Table 3. Multivariate-adjusted[a] odds ratios for cause-specific and all-cause mortality by glucose tolerance status in 1984

Glucose tolerance status	Cardiovascular deaths		Cancer deaths		Other deaths		All deaths	
	Odds ratio[a]	(95 % CI)	Odds ratio[a]	(95 % CI)	Odds ratio[a]	(95 % CI)	Odds ratio[a]	(95 % CI)
Normal	1		1		1		1	
Impaired	1.13	(0.62, 2.08)	0.69	(0.29, 1.54)	2.02	(0.71, 5.74)	1.17	(0.71, 1.94)
Diabetes	1.55	(0.84, 2.85)	1.52	(0.68, 3.39)	2.48	(0.88, 6.98)	2.10	(1.26, 3.49)
Diabetes by treatment								
– diet alone[b]	1.43	(0.74, 2.75)	1.52	(0.64, 3.58)	2.06	(0.67, 6.29)	1.80	(1.05, 3.10)
– hypoglycaemic agents	1.93	(0.81, 4.61)	1.55	(0.48, 5.01)	3.71	(1.03, 13.40)	3.46	(1.58, 7.57)

[a] Adjusted for age, body mass index, hypertension, smoking history, total and HDL cholesterol and functional capacity
[b] Includes both newly-diagnosed diabetic patients and known diabetic patients treated with diet alone. 95 % CI, 95 % confidence interval

Table 4. Age-specific 5-year cardiovascular and total mortality rates and odds ratios by glucose tolerance status at baseline

Age group and glucose tolerance status	Number of men	Cardiovascular deaths				All deaths			
		Number of deaths	Rate per 1000 men	Odds[a] ratio	(95 % CI)	Number of deaths	Rate per 1000 men	Odds[a] ratio	(95 % CI)
Age 65 to 74 years									
Normal	168	12	71	1		25	149	1	
Impaired	155	18	116	1.56	(0.70, 3.48)	28	181	1.29	(0.68, 2.44)
Diabetes	105	16	152	2.35	(1.01, 5.46)	29	276	2.33	(1.19, 4.54)
Age 75 to 84 years									
Normal	48	11	229	1		17	354	1	
Impaired	79	14	177	0.67	(0.24, 1.58)	28	354	1.00	(0.44, 2.67)
Diabetes	82	20	244	1.24	(0.32, 2.02)	44	537	1.84	(0.81, 4.17)

[a] Adjusted for age within age group and for body mass index, hypertension, smoking history, total- and HDL cholesterol and functional capacity. 95 % CI, 95 % confidence interval

Discussion

The impairment of glucose tolerance with advancing age is a well-known phenomenon first reported by Spence in 1920 [26]. According to recent studies a large proportion of elderly subjects aged 65 years and over have either impaired glucose tolerance or overt diabetes [22, 27]. However, prognostic importance of diabetes in the elderly is not very well established. There is some evidence that the excess mortality risk in diabetic patients diminishes with advancing age and may even disappear at about 75 years of age [2, 6]. A similar age-specific trend was also seen in this study. However, in agreement with some other earlier findings [9, 10], our results showed that diabetes is an important predictor of death among elderly men.

We followed a cohort of elderly Finnish men aged 65 to 84 years for 5 years. Both diabetes and impaired glucose tolerance were common among these men at baseline [22]. Approximately one-third of the diabetic patients died during the follow-up. The overall mortality risk of these men was twice as high as in men with normal glucose tolerance after the adjustment for age and several major risk factors for chronic diseases. This estimate is relatively high compared with the results of previous studies from other populations where mortality risks have been reported to range usually from 1.0 to 1.4 [2, 4, 6–8] among diabetic subjects of the same age. In one earlier study of elderly Finnish men no association between self-reported diabetes and increased mortality was found [28]. There are, however, some methodological differences between previous surveys and our study.

Definition of diabetes in many previous studies was based on self-reported history of diabetes in a questionnaire survey [19, 28], or they were drawn from a hospital series [2, 8, 9] or from a special diabetes registry [6–8]. Self-reported diabetes is, however, subject to several misclassification biases. Madow [29] found that approximately 15 % of the people who had diabetes according to their medical record did not report their disease. On the other hand, approximately 14 % of the self-reported diabetic patients in the Second National and Nutrition Examination Survey in the United States were not diabetic but

Table 5. Number of deaths, due to causes other than cardiovascular disease or cancer

Causes of death	Glucose tolerance status		
	Diabetes ($n = 187$)	Impaired ($n = 234$)	Normal ($n = 216$)
Infection	8	9	2
– pneumonia	5	8	2
– pyelonephritis	1	1	0
– septicaemia	1	0	0
– pleuritis	1	0	0
Accident	3	1	2
Embolia pulmonum	1	2	0
Oedema pulmonum	0	1	0
Volvulus sigmae	0	1	0
Diabetes mellitus	1	–	–
Unclassifiable	5	0	2
Total	18	14	6

were misdiagnosed or incorrectly reported themselves as diabetic patients [30]. Furthermore, a section of elderly diabetic subjects are not aware of their disease because it is often asymptomatic. The former biases can be avoided if the diagnosis of diabetes is based on an oral glucose tolerance test, which has been used in many studies where diabetic subjects were drawn from a registry. The use of registries, however, often brings in such other biases as a selection bias or a referral bias [4, 31]. For instance, many diabetic patients included in diabetes registries have a relatively severe disease which requires treatment with either oral anti-diabetic drugs or insulin. Risk estimates derived from such a patient material will be likely to be higher than those obtained in diabetic patients treated with diet only. On the other hand, relative risk estimates for mortality in these kinds of studies are often calculated either in comparison with the general population or recruiting the referent subjects from other hospital clinics. Such reference groups can also include diabetic subjects, which may lower the estimated relative risks.

In some earlier studies mortality estimates among diabetic subjects were based on a review of routine death certification data [1, 4]. Lack of reliability and validity of death certificates serves as a major source of bias in such studies [4, 32]. For instance, Fuller and co-workers [32] reported that diabetes was not mentioned in 33 % of death certificates of known diabetic patients. These kinds of biases are less common in well-designed prospective cohort studies, where both death certificates and hospital records are systematically collected. On the other hand, large prospective cohort studies may face problems in mortality follow-up since among the "survivors" there may be subjects whose vital status is not exactly known.

We tried to avoid known biases by testing glucose tolerance of all responders at baseline, except subjects receiving anti-diabetic medication and those whose fasting blood glucose exceeded 10 mmol/l. Thus, normal glucose tolerance status was also ascertained with the glucose tolerance test. Furthermore, mortality follow-up in our study was complete. On the other hand, there were 129 men who we could not classify according to their glucose tolerance status at baseline. Most of them were chronically ill and 55 % of them died between 1984 and 1989. The contribution of diabetes to their mortality is not known.

The relative risk of dying among patients using anti-diabetic drugs was twice as high as that in diabetic patients treated with diet alone. The risk was particularly increased in insulin-treated subjects. It is most likely that elderly individuals whose glycaemic control required insulin treatment had more severe disease than those who were satisfactorily treated with oral anti-diabetic drugs or diet alone. Thus, our results support earlier findings that the severity of diabetes predicts mortality among diabetic patients [1, 9].

Cardiovascular disease is the most common underlying cause of death among Caucasoid diabetic patients as has been previously shown in several studies [2, 4, 5, 8, 10–14]. In our study approximately one-half of the deaths in diabetic men were from cardiovascular diseases. Diabetes doubled the age-specific risk of cardiovascular death among men aged below 75 years, but it was not associated with excess risk among older men. Overall, in the diabetes group the risk of death from cardiovascular disease was 50% higher compared with men with normal glucose tolerance. Due to the relatively small study population the 95% CI was wide and the risk estimate did not reach statistical significance. However, the excess in absolute mortality from cardiovascular disease in diabetic men was 66 deaths per 1000 men during the 5-year period compared with men with normal glucose tolerance. This indicates that diabetes is a significant determinant for cardiovascular death among elderly men. On the other hand, diabetes alone may not be sufficient for the increased risk of coronary heart disease, because in Pima Indians coronary mortality is not particularly high despite the extremely high prevalence of diabetes [33].

Relative risks of death from other, non-cardiovascular causes tended also to be increased among diabetic subjects. Particularly, mortality from infectious diseases seemed to be greater among subjects with diabetes or impaired glucose tolerance suggesting that abnormal glucose tolerance may increase susceptibility to infections.

Both overall mortality rate and mortality rate from cardiovascular disease in subjects with impaired glucose tolerance have been found to be between that of diabetic patients and non-diabetic patients [16]. Also in our study mortality rates from cardiovascular disease and from all causes were intermediate among men with impaired glucose tolerance. However, the mortality risk estimates did not differ significantly from those obtained in subjects with normal glucose tolerance. This may partly reflect the heterogeneity of the impaired glucose tolerance category. Furthermore, several environmental and host factors may cause misclassification by the glucose tolerance test. Among subjects with impaired glucose tolerance the result of the glucose tolerance test has been found to be normal in 10% to 60% in a repeated test [34]. In our study the definition of impaired glucose tolerance was based on a single glucose tolerance test, many of which were performed in the afternoon. Thus, some subjects with normal glucose tolerance may have been falsely included in the impaired glucose tolerance category in our study, underestimating the importance of impaired glucose tolerance.

In conclusion, our study shows that diabetes is a significant determinant of mortality among elderly men in Finland. Every third diabetic man but only every fifth man with normal glucose tolerance in our cohort died during the 5-year follow up. Most of the deaths were from cardiovascular disease. These findings suggest that diabetes is an important public health problem among elderly subjects, and likely to increase in importance in all populations where the proportion of elderly people is now rapidly increasing.

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Dr. J. H. Stengård
National Public Health Institute
Department of Epidemiology and health promotion
Elimäenkatu 25 A, 6th floor
SF-00510 Helsinki
Finland