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RESEARCH

Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study

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ABSTRACT

Objective To examine trends in fatal coronary heart disease in adults with and without diabetes.

Design Cohort study.

Setting Two surveys of the Nord-Trøndelag health study (HUNT), a population based study in Norway.

Participants 74 914 men and women from the first survey (1984-6) and 64 829 from the second survey (1995-7).

Main outcome measure Age specific mortality from coronary heart disease among adults with and without diabetes during two consecutive nine year follow-up periods.

Results A total of 2623 men and 1583 women died from coronary heart disease. Mortality rates were substantially lower during the most recent follow-up period: among men aged 70-79 without diabetes, deaths per 1000 person years declined from 16.38 to 8.79 (reduction 48%, 95% confidence interval 39% to 55%) and among women aged 70-79 from 6.84 to 2.68 (62%, 52% to 70%). Among the same age group with diabetes, deaths per 1000 person years in men declined from 38.97 to 17.89 (54%, 32% to 69%) and in women from 28.15 to 11.83 (59%, 37% to 73%). The reduction was more noticeable in age groups younger than 70 at baseline, and less pronounced among people aged 80 or more. Mortality from coronary heart disease was more than twofold higher in people with than without diabetes, with a slightly stronger association in women. The difference in mortality by diabetes status remained almost unchanged from the first to the second survey.

Conclusion The strong general reduction in mortality rates from coronary heart disease from the first to the second follow-up period also benefited people with diabetes, but the more than twofold higher mortality from coronary heart disease associated with diabetes persisted over time.

INTRODUCTION

Mortality rates from coronary heart disease have declined in the Western world[1-5] during the past 30 years, most rapidly from the mid-1980s, and faster in men than in women. The reason for the decrease includes a reduced burden of risk factors related to cardiovascular disease,[6] a lower incidence of coronary heart disease, and improved survival as a result of better treatment.[1 5 7-11] Over the same timespan the incidence and prevalence of diabetes have increased.[12-19] Compared with the general population, people with diabetes have a 2-4-fold higher mortality from coronary heart disease,[20] but many studies have also shown a secular decline in mortality from coronary heart disease in people with diabetes,[19 21-23] although the evidence for this is not supported by all studies.[24 25]

We compared mortality rates from coronary heart disease over two consecutive nine year periods in adults who reported diabetes in the 1980s and in the 1990s. We also studied mortality rates from coronary heart disease among adults without diabetes.

METHODS

Two large population surveys were carried out in Nord-Trøndelag county, Norway: the first wave (HUNT 1) in 1984-6 and the second wave (HUNT 2) in 1995-7. Nord-Trøndelag is in the middle of Norway and is regarded as fairly representative of the country. The population is stable and ethnically homogeneous, with only a small percentage (3%) of people of non-white origin. In both studies residents aged 20 years or older were invited to participate. A total of 74 977 (88.1%) adults participated in the first survey and 66 140 (71.2%) in the second survey.

Participants in the first survey responded to a questionnaire and attended a clinical examination that included measurements of blood pressure, pulse, body weight, and height.[26] In the present analysis we included 74 914 people (36 722 men and 38 192 women; a total of 2100 reported to have diabetes) who had valid responses to the variables of body weight, height, systolic and diastolic blood pressure, and diabetes status.

Participants in the second survey completed a more comprehensive questionnaire than in the first survey.[27] In the analysis we included 64 829 people (30 367 men and 34 462 women; a total of 1951 reported to have diabetes) who responded to the questionnaire, attended the clinical examination, and had valid data on body weight, height, systolic and diastolic blood pressure, and diabetes status.

Definitions

From the baseline questionnaire we collected information on prevalent diabetes and history of

Table 1 | Baseline characteristics of two cohorts of Nord-Trøndelag health study. Bracketed values are 95% confidence intervals unless stated otherwise

	Diabetes		No diabetes	
Characteristics	First survey	Second survey	First survey	Second survey
Men:				
No (% of total)	932 (2.5)	940 (3.1)	35 790 (97.5)	29 427 (96.9)
Mean age (years)	66.2 (65.3 to 67.1)	64.3 (63.4 to 65.2)	48.5 (48.3 to 48.7)	49.3 (49.1 to 49.5)
Mean glucose* level (mmol/l)	8.6 (8.4 to 8.9)	10.0 (9.7 to 10.3)	5.5 (5.5 to 5.5)	5.4 (5.4 to 5.4)
Mean body mass index (kg/m^2)	26.3 (26.0 to 26.5)	28.0 (27.7 to 28.2)	25.2 (25.2 to 25.2)	26.4 (26.4 to 26.4)
Mean systolic blood pressure (mm Hg)	154.0 (152.3 to 155.7)	150.8 (149.4 to 152.3)	141.2 (140.9 to 141.4)	139.7 (139.5 to 140.0)
% hypertensive†	53.4 (50.2 to 56.7)	51.4 (48.1 to 54.6)	33.3 (32.8 to 33.8)	26.0 (25.5 to 26.5)
% current smokers	21.5 (18.9 to 24.2)	20.3 (18.8 to 23.0)	30.8 (30.3 to 31.2)	28.4 (27.9 to 29.0)
% obese‡	14.6 (12.4 to 17.0)	27.6 (24.7 to 30.5)	7.5 (7.2 to 7.8)	13.8 (13.4 to 14.2)
% with baseline cardiovascular disease§	28.8 (25.9 to 31.8)	31.5 (28.5 to 35.6)	7.6 (7.3 to 7.9)	9.3 (9.0 to 9.6)
Women:				
No (% of total)	1 168 (3.1)	1 011 (2.9)	37 024 (96.6)	33 451 (96.9)
Mean age (years)	69.8 (69.1 to 70.5)	67.6 (66.7 to 68.4)	49.4 (49.2 to 49.6)	49.6 (49.4 to 49.7)
Mean glucose* (mmol/l)	8.4 (8.2 to 8.7)	9.2 (9.0 to 9.5)	5.1 (5.1 to 5.1)	5.3 (5.3 to 5.3)
Mean body mass index (kg/m^2)	28.0 (27.7 to 28.3)	29.9 (29.6 to 30.3)	25.0 (25.0 to 25.1)	26.2 (26.1 to 26.2)
Mean systolic blood pressure (mm Hg)	163.8 (162.1 to 165.4)	157.3 (155.7 to 158.9)	138.1 (137.8 to 138.4)	135.3 (135.1 to 135.6)
% hypertensive†	64.4 (61.6 to 67.1)	57.2 (54.1 to 60.2)	30.9 (30.4 to 31.4)	22.2 (21.7 to 22.6)
% current smokers	9.3 (7.7 to 11.1)	12.4 (10.4 to 14.6)	25.8 (25.4 to 26.3)	29.3 (28.8 to 29.8)
% obese‡	31.2 (28.5 to 33.9)	43.8 (40.7 to 46.9)	12.8 (12.5 to 13.2)	17.6 (17.2 to 18.0)
% with baseline cardiovascular disease§	28.1 (25.5 to 30.8)	25.8 (23.1 to 28.6)	5.0 (4.8 to 5.2)	5.5 (5.2 to 5.7)

*Random measurement.
†Systolic blood pressure ≥140/90 mm Hg or taking antihypertensive drugs.
‡Body mass index ≥30.0 kg/m^2.
§Known angina, stroke, or myocardial infarction, as reported at baseline.

cardiovascular disease. We defined those who responded positively to the question "Do you have or have you had diabetes?" to have diabetes. Participants were specifically asked about history of angina, myocardial infarction, and stroke, and we classified those who responded positively to one or more relevant questions as having established cardiovascular disease.

Body mass index was calculated as weight (kg) divided by the squared value of height (m) and classified according to the definitions of the World Health Organization (<18.5 kg/m^2=underweight, 18.5-24.9 kg/m^2=normal weight, 25-29.9 kg/m^2=overweight, ≥30 kg/m^2=obesity). Random non-fasting glucose (mmol/l) was measured in participants aged 40 or more. We defined hypertension as a blood pressure of 140/90 mm Hg or more or as current use of antihypertensive drugs. Exercise as reported in the first survey was divided into three levels; no regular exercise, exercise once weekly, and exercise twice or more weekly. Exercise reported in the second survey was categorised into four levels; no regular exercise, 2-3 hours of light weekly activity, three hours of light activity or one hour of hard activity weekly, and more than one hour of hard activity weekly. On the basis of self reporting of smoking status, participants were classified into three categories: current smoker, former smoker, or never smoker. We dichotomised education according to duration: less than 13 years or 13 or more years.

Follow-up

We obtained information on causes of death by linking data from the first and second surveys to the Causes of Death Registry at Statistics Norway, which receives the death certificates of all Norwegian citizens. Deaths were classified according to the international classification of diseases (ninth and 10th revisions, respectively): coronary heart disease 410-4 and I20-5, cardiovascular disease 390-459 and I00-99, and stroke 430-8 and I60-69.9.

For the follow-up of mortality after the first survey, we calculated individual person time from the date of participation at baseline (1984-6) until date of death from coronary heart disease or from other causes, or until the end of follow-up on 31 December 1993. Follow-up after the second survey was calculated as person time from the date of participation at baseline (1995-7) until date of death from coronary heart disease or from other causes, or until the end of follow-up on 31 December 2004.

Statistical analysis

We calculated age specific mortality rates from coronary heart disease among men and women with and without diabetes during nine years of follow-up after both the first survey and the second survey. A Mantel-Cox comparison was used to calculate mortality rate ratios, with 95% confidence intervals, between the two follow-up periods by sex, age group, and diabetes status.

We also estimated hazard ratios (95% confidence intervals) of mortality from coronary heart disease between people with and without diabetes. The analysis was done separately for each follow-up period for the whole population and stratified by sex, using

Cox regression analysis. Analyses were adjusted for age (continuous), body mass index (continuous), hypertension (yes, no), smoking status (current, former, never or unknown), exercise level (none, regular, unknown), and level of education (low, high, unknown). We tested for statistical interaction between study period (first survey or second survey) and prevalence of diabetes in relation to mortality from coronary heart disease during follow-up. Departure from the proportional hazards assumption was evaluated using graphical procedures (log-log plots). We used Stata for Windows (version 9.2) and SPSS for Windows (version 14) for the statistical analyses.

RESULTS

In men the prevalence of diabetes was higher in the second survey than in the first survey, whereas in women the prevalence of diabetes did not increase over time (table 1). Among those with diabetes, mean body mass index was about two units higher in the second than in the first survey. Among those without diabetes mean body mass index was about one unit higher in the second than in the first survey. Systolic blood pressure in the second survey was generally lower in all groups, with the greatest reduction in people with diabetes. A lower proportion of men but higher proportion of women reported current smoking in the second survey.

During the two follow-up periods 15 365 people died (table 2). The proportion of deaths from coronary heart disease among people with diabetes at baseline decreased from the first to the second survey (men, 19.7% to 10.3%; women, 18.2% to 8.2%). Among people without diabetes at baseline, a similar reduction occurred in the proportion of deaths caused by coronary heart disease from the first to the second survey (men, 4.6% to 2.4%; women, 2.4% to 1.2%).

Among people without diabetes, mortality rates from coronary heart disease were substantially lower during the follow-up period after the second survey (1995-2004) than after the first survey (1984-93), and among men the reduction in mortality rates from coronary heart disease was more pronounced in younger age groups (table 3). Thus in people without diabetes at baseline the mortality rate from coronary heart disease in men aged 70-79 declined from 16.38 to 8.79 deaths per 1000 person years (reduction 48%, 95% confidence interval 39% to 55%) and in women aged 70-79, it declined from 6.84 to 2.68 deaths per 1000 person years (reduction 62%, 52% to 70%). In people with diabetes at baseline the mortality rate from coronary heart disease in men aged 70-79 declined from 38.97 to 17.89 deaths per 1000 person years (reduction 54%, 32% to 69%) and in women aged 70-79 declined from 28.15 to 11.83 deaths per 1000 person years (reduction 59%, 37% to 73%). From the first survey to the second survey the reduction in mortality from coronary heart disease was stronger in age groups younger than 70 at baseline and less pronounced among those aged 80 or more (table 3). Mortality rates in women generally resembled those in men about 10 years younger.

The higher mortality associated with diabetes was roughly the same for both follow-up periods (adjusted hazard ratio 2.48, 95% confidence interval 2.19 to 2.81 *v* 2.24, 1.91 to 2.64). In sex specific analyses, the association of diabetes with mortality from coronary heart disease was slightly stronger in women than in men for both follow-up periods. Thus the hazard ratios for women with diabetes at baseline compared with those without diabetes at baseline were 2.87 (2.39 to 3.44) after the first survey and 2.71 (2.12 to 3.47) after the second survey. In men the corresponding values were 2.16 (1.81 to 2.57) and 1.95 (1.57 to 2.42; table 4).

DISCUSSION

We found a strong and general decline in mortality rates from coronary heart disease irrespective of age, sex, and diabetes status during two consecutive nine years of follow-up after the first and second surveys of the Nord-Trøndelag health study. Throughout the two follow-up periods mortality from coronary heart disease in people with diabetes at baseline was more than twofold higher than in those without diabetes at baseline, even if the population with diabetes experienced a reduction in mortality rates from coronary heart disease similar to that of the general population.

In agreement with other studies we found that people who reported diabetes in the most recent cohort (second survey) were on average younger[15 28] and the prevalence of diabetes was higher than in the cohort from the first survey. Hypertension was more prevalent in people with diabetes. This might partly explain the increased risk for coronary heart disease associated with diabetes.[6 29 30] The prevalence of hypertension decreased from the first survey to the second, but in the second survey still more than half the population with

Table 2 | Total deaths and deaths from coronary heart disease during nine years of follow-up of both first and second surveys of Nord-Trøndelag health study. Values are numbers (percentage of people in each cell; 95% confidence interval)

	Diabetes		No diabetes	
Variables	First survey	Second survey	First survey	Second survey
Men:				
Deaths	487 (52.3; 49.0 to 55.5)	313 (33.3; 30.3 to 36.4)	4 893 (13.7; 13.3 to 14.0)	2 879 (9.8; 9.4 to 10.1)
Coronary heart disease deaths	184 (19.7; 17.2 to 22.4)	97 (10.3; 8.4 to 12.4)	1 638 (4.6; 4.4 to 4.8)	704 (2.4; 2.2 to 2.6)
Women:				
Deaths	598 (51.2; 48.3 to 54.1)	352 (34.8; 31.9 to 37.8)	3 537 (9.6; 9.3 to 9.9)	2 306 (6.9; 6.6 to 7.2)
Coronary heart disease deaths	212 (18.2; 16.0 to 20.5)	83 (8.2; 6.6 to 10.1)	883 (2.4; 2.2 to 2.5)	405 (1.2; 1.1 to 1.3)

Table 3 | Mortality rates from coronary heart disease after nine years' follow-up of both first and second surveys of Nord-Trøndelag health study, and mortality rate ratios from coronary heart disease after second versus first survey

Age (years) at baseline	First survey			Second survey			Rate ratios (95% CI) second *v* first survey
	Person years	No of deaths	Mortality rate* (95% CI)	Person years	No of deaths	Mortality rate* (95% CI)	
Men							
No diabetes:							
<60	199 282	152	0.76 (0.65 to 0.89)	159 942	41	0.26 (0.19 to 0.35)	0.26 (0.19 to 0.37)
60-69	50 175	364	7.25 (6.55 to 8.04)	35 127	83	2.36 (1.91 to 2.93)	0.33 (0.26 to 0.42)
70-79	36 620	600	16.38 (15.12 to 17.75)	30 025	264	8.79 (7.79 to 9.92)	0.52 (0.45 to 0.61)
≥80	14 684	520	35.41 (32.50 to 38.59)	13 453	316	23.49 (21.04 to 26.23)	0.67 (0.59 to 0.77)
Diabetes:							
<60	1525	7	4.59 (2.19 to 9.63)	1992	1	0.50 (0.07 to 3.56)	0.07 (0.01 to 0.84)
60-69	1464	45	30.73 (22.95 to 41.16)	1440	11	7.70 (4.26 to 13.90)	0.27 (0.14 to 0.52)
70-79	1925	75	38.97 (31.08 to 48.87)	2068	37	17.89 (12.97 to 24.70)	0.46 (0.31 to 0.68)
≥80	1119	56	50.07 (38.53 to 65.06)	1096	48	43.79 (33.00 to 58.10)	0.92 (0.62 to 1.36)
Women							
No diabetes:							
<60	200 991	28	0.14 (0.10 to 0.20)	179 967	4	0.02 (0.01 to 0.06)	0.13 (0.05 to 0.38)
60-69	52 072	87	1.67 (1.35 to 2.06)	38 796	35	0.90 (0.65 to 1.26)	0.56 (0.38 to 0.83)
70-79	43 588	298	6.84 (6.10 to 7.66)	35 404	95	2.68 (2.19 to 3.28)	0.38 (0.30 to 0.48)
≥80	21 590	468	21.68 (19.80 to 23.73)	21 480	271	12.62 (11.20 to 14.21)	0.59 (0.50 to 0.68)
Diabetes:							
<60	1160	2	1.72 (0.43 to 6.89)	1587	1	0.63 (0.09 to 4.47)	0.26 (0.02 to 3.85)
60-69	1645	25	15.20 (10.27 to 22.50)	1173	2	1.71 (0.43 to 6.68)	0.12 (0.03 to 0.51)
70-79	2842	80	28.15 (22.61 to 35.04)	2367	28	11.83 (8.17 to 17.13)	0.41 (0.27 to 0.63)
≥80	2014	104	51.63 (42.60 to 62.57)	2125	52	24.47 (18.65 to 32.12)	0.50 (0.36 to 0.71)

*Per 1000 person years.

diabetes had hypertension. This suggests that antihypertensive treatment in people with diabetes could have improved during the past decades and that people with diabetes could have benefited both in relation to cardiovascular complications and cardiovascular death. None the less, indications are that further improvements in the treatment of hypertension could still be achieved.[29 31]

From the first survey to the second the prevalence of obesity (body mass index >30) increased in all groups, but this increase was more noticeable in men than in women. Similar observations have been made in other populations.[9 32] In our study, obesity was twice as prevalent in people with diabetes and more prevalent in women than in men with diabetes. Obesity increases the risk for diabetes,[9 13 14 18 33] and obesity, either alone or in combination with diabetes, increases the risk of mortality from coronary heart disease, although the increase seems to be moderate.[34] It would therefore be expected that the higher prevalence of obesity in the second survey would yield a slightly higher risk of fatal coronary heart disease than after the first survey. Our results, however, suggest the opposite: women with diabetes showed the largest reduction in mortality rates from coronary heart disease from the first survey to the second survey. This seemingly paradoxical finding could have several explanations. A sharp increase in body mass index has occurred during recent years and follow-up in our study may not be sufficiently long to capture the influence of the general weight gain. Also, widespread use of more effective medical treatment[9 10 35] after the second survey may have resulted in lower blood pressure and lower prevalence of other risk factors[6] and could have outweighed the

Table 4 | Hazard ratios of death from coronary heart disease in people with diabetes compared with people without diabetes, by sex, during nine years' follow-up of both first and second surveys Nord-Trøndelag health study

Variable	Men		Women	
	Age and sex adjusted hazard ratio (95% CI)	Multivariable* adjusted hazard ratio (95% CI)	Age and sex adjusted hazard ratio (95% CI)	Multivariable* adjusted hazard ratio (95% CI)
First survey:				
No diabetes	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Diabetes	2.11 (1.81 to 2.46)	2.16 (1.81 to 2.57)	3.19 (2.74 to 3.72)	2.87 (2.39 to 3.44)
Second survey:				
No diabetes	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Diabetes	2.03 (1.64 to 2.51)	1.95 (1.57 to 2.42)	2.53 (2.0 to 3.2)	2.71 (2.12 to 3.47)

*Adjusted for age, sex, hypertension, body mass index, smoking, exercise, and education.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Mortality rates from coronary heart disease have declined in the Western world during the past 30 years, most rapidly from the mid-1980s

People with diabetes have a 2-4-fold higher mortality from coronary heart disease

WHAT THIS STUDY ADDS

The strong general decline in mortality coronary heart disease has also benefited people with diabetes

The more than twofold higher risk of dying from coronary heart disease in men and women with diabetes has persisted over time

relatively weak[34] effect of the higher prevalence of obesity.

The proportion of men who were current smokers decreased from the first survey to the second survey, irrespective of diabetes status, whereas the proportion of women who were current smokers increased. Smoking status therefore cannot explain the decline in fatal coronary heart disease among women with diabetes in this study.

People with diabetes have a higher burden of risk factors for cardiovascular disease than those without diabetes. Despite adjustment for conventional risk factors,[36] our results showed that people with diabetes still had more than a twofold higher mortality from coronary heart disease.

Other studies have also shown that mortality from coronary heart disease has decreased over the past decades, and it seems that patients with diabetes have also benefited from this reduction.[19 21-23] We found a reduction in mortality rates over time for both men and women with diabetes, and our results are consistent with those of others.[21 22 24 25] One study,[24] however, found only a moderate reduction in mortality from coronary heart disease in men with diabetes, whereas another study[21] reported a greater reduction in people with diabetes. The decline in mortality from coronary heart disease that we found for women with diabetes is consistent with some[21] but not with other studies.[24 25]

In our study a particularly noticeable reduction in mortality from coronary heart disease from the first follow-up period to the second follow-up occurred in younger age groups. A relatively lower reduction in older age groups has also been observed by others,[22-24] but some studies found that all age groups have gone through a period with similar reduction in mortality from coronary heart disease.[35] Our finding could reflect age as a dominant factor but also that less intensive primary and secondary prevention is applied to elderly people.[37] It is also possible that both incidence and case fatality from cardiovascular disease could have been reduced as a result of better primary prevention and more effective treatment, and that people with prevalent cardiovascular disease now experience longer survival than before.

The awareness of the higher cardiovascular risk associated with diabetes and impaired glucose tolerance has probably intensified cardioprotective treatment in these patients. Lower mortality may be a result of several factors, including a reduced burden of risk factors,[9 35] lower incidence of acute myocardial infarction,[3 8 38] improved treatment in the acute phase of coronary events,[8 10 39] and longer survival resulting from aggressive secondary prevention.[3 8 38 40] The exact impact of each of these factors is not clear,[7] but it was recently estimated [9 35] that 42-47% of the decline in mortality from coronary heart disease from 1980 to 2000 can be explained by evidence based therapies, mostly related to secondary prevention after acute myocardial infarction, followed by improved treatment during the acute phase of coronary syndromes. Between 44% and 58% of the reduction was attributed to a reduced burden of risk factors, although this reduction may partly be offset by the increase in mortality from coronary heart disease resulting from the increase in body mass index and prevalence of diabetes.[9 35] The observation period of the present study coincides with changes in treatment[9 35 39 40] that could have contributed to the decline in mortality from coronary heart disease, irrespective of diabetes status.

Our study has some limitations. Diabetes was defined by self reporting and this could be a source of misclassification. A separate study based on the data from the Nord-Trøndelag health study, however, showed that self reported diabetes was correct in 96.5% of the cases.[41] Other studies have also shown that self reporting of diabetes is valid in most cases.[42 43] From the start of the first survey to the end of follow-up after the second survey the prevalence of diabetes increased in the general population, although mean random glucose levels in people who reported diabetes were not substantially different in either survey. None the less, a proportion of people without known diabetes at baseline probably developed the disease during follow-up, but we could not take this change in disease status into account in the analysis. It should also be noted that a change in the definition of death from coronary heart disease occurred from the first follow-up period to the second follow-up period. This should not, however, affect the mortality ratio between people with and without diabetes within the same follow-up period.

We found that during follow-up of mortality over two consecutive nine year periods, the risk of death from coronary heart disease was more than twofold higher in people with diabetes. We also found that mortality rates from coronary heart disease decreased substantially in all age groups irrespective of sex and diabetes status. This suggests that people with diabetes have also benefited from the overall decline in mortality from coronary heart disease.

Nord-Trøndelag health (HUNT) study is a collaboration between HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology, the Norwegian Institute of Public Health, and Nord-Trøndelag county council.

Contributors: KM was responsible for the original collection of data and interpreted the findings. ACD and RW conceived the article, analysed the data, and wrote the paper. LJV and TIN analysed and interpreted the data and wrote the paper. RW is guarantor of the study.

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