ORIGINAL ARTICLE

Secular decrease in blood pressure and reduction in mortality from cardiovascular disease in Israeli workers

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The reasons for the dramatic reduction in age-adjusted mortality from cardiovascular disease (CVD) since the 1970s in developed countries remain uncertain. In the following study we compare the cardiovascular and all-cause mortality rates over an 11-year period in two well-defined employed male cohorts aged 40–69 years old recruited 24 years apart. Blood pressure and other risk markers for CVD were assessed at the time of inception (1963 for 10048 male civil servants and 1985–1987 for 2237 male industrial workers). Compared to the 1987 cohort, the 1963 cohort show an increase of 8.7 mmHg in the mean systolic blood pressure (SBP) (95% confidence interval (CI): 7.7, 9.6) and a concomitant hazard

ratio for CVD mortality of 1.47 (95% CI: 1.16, 1.87). After adding SBP to the analysis, the hazard ratio for CVD mortality in the 1963 cohort decreased to 1.18 (95% CI: 0.88, 1.43). Adding the other risk modifiers to the analysis did not modify the hazard ratio to the same extent. Similar results were obtained for all-cause mortality. We conclude that declining blood pressure values are a major factor in explaining the secular decrease in CVD mortality over a period of 24 years in Israel.

Journal of Human Hypertension (2004) 18, 113–118.
doi:10.1038/sj.jhh.1001645

Keywords: cardiovascular disease mortality; secular change; blood pressure; workers; risk factors

Introduction

A dramatic reduction in age-adjusted mortality from cardiovascular disease (CVD) since the 1970s years has been well documented in most Western countries.¹ Mortality from CVD has declined by more than 50% and the downward trend is continuing.² Explanations for this remain uncertain. Many attribute most of the CVD mortality rate fall to reductions in major risk factors such as smoking, cholesterol and blood pressure.^{3,4} Others believe that the dominant influence is the combination of improved care of patients with established CVD and the prevention of recurrent coronary events.^{1,5}

One of the important components might be the reduction in blood pressure reported both in Europe^{6,7} and the United States.⁸ Blood pressure is a consistent risk marker for CVD mortality, with an estimated relative risk of death due to CVD of 2–4%

for every increase of 1 mmHg in systolic blood pressure (SBP).^{9–12} Since a reduction in SBP of around 10 mmHg has been observed over periods of 25–30 years in both Europe and the United States,^{6–8} this degree of reduction might account for 20–40% reduction in CVD mortality, explaining 40–80% of the approximate 50% reduction in CVD mortality. Such calculations assume that the observed associations of SBP with CVD mortality can be extrapolated to secular changes and that the association of SBP with death due to CVD has remained constant over time.

In the following study, we compare the cardiovascular and all-cause mortality rates over an 11-year period in two well-defined employed male cohorts aged 40–69 years recruited 24 years apart who had blood pressure and other risk markers for CVD assessed at the time of inception.

Materials and methods

Study populations

The Israeli Ischemic Heart Disease (IIHD) project recruited male civil servants and municipal

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Received 10 May 2003; revised 18 August 2003; accepted 18 August 2003

employees aged 40 years or above working in Jerusalem, Tel-Aviv and Haifa, and examined 10 048 males aged 40–69 years chosen according to birth stratification during the course of a survey conducted in 1963.¹³ The response rate to the initial examination was 86.2%. Between 1985 and 1987, the Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) study examined 4318 male employees of 21 factories in Israel. The response rate was 70%,¹⁴ and there were 2237 workers between the age of 40 and 69 years.

Risk modifiers

Blood pressure was measured three times in both the studies. We used the first measurement, since it was performed in the supine position in both the studies^{13,15} using a standard mercury sphygmomanometer with a 12-cm diameter cuff on the right arm. In the IIHD study, it was recorded by physicians around 30–45 min after arrival, while in the CORDIS study, blood pressure was measured by technicians after the subject had been resting for 5 min.¹⁵

Nonfasting blood samples in the IIHD were drawn in the morning, kept refrigerated and shipped daily in ice-cooled containers to a central laboratory. In the CORDIS, venous blood samples were drawn after a fast of at least 8 h between 6 and 9 in the morning.

The IIHD used the Anderson and Keys modification of the Abel method¹⁶ to measure serum cholesterol. The control procedures included the use of freshly weighed standards, daily determination of a specimen derived from pooled adult human serum and duplicate tests on all specimens. The cholesterol value reported for each individual was the average of duplicate testing with a coefficient of variation of around 2.4%. The CORDIS used an enzymatic colour method (Lancer) to measure serum cholesterol, and standardized through the lipid reference laboratory of the MONICA project of the World Health Organization with an average coefficient of variation of 3%.¹⁷

Other variables included drugs for diabetes mellitus (yes/no), regular leisure physical activity defined as all activities defined by the worker as regular and not sporadic (yes/no), education of at least 12 years (high school equivalent) (yes/no), persons per room (family members divided by number of rooms in the house), and body mass index (BMI) (weight in kilograms divided by height in metres squared).

Mortality

The IIHD project ascertained deaths from information from the Israeli mortality Registry. For all hospital deaths until 1970, comparison of death certificates with the analyses of hospital records (including physician notes, autopsy reports and

death certificates) by a study panel revealed a >90% agreement. The physician analysis of a 254 random sample of hospital deaths vs death certificates showed an agreement of almost 100% of deaths due to cancer, and an 84% proportion of agreement for deaths due to nonmalignant disease. The CORDIS used the same mortality registry, examined all death certificates and obtained information from the National cancer registry. We have shown previously that the registry is 91% accurate in dividing the deaths into three categories (CVD, cancer, other) and after contacting the homes of 2630 men in the cohort found that the registry did not miss any deaths.¹⁴ The follow-up periods were 1963–1973 for the IIHD and 1987–1997 for the CORDIS.

Statistical analysis

Proportions, means, standard errors (s.e.), differences between the two cohorts and 95% confidence intervals (CIs) of the differences were calculated with adjustment for age (years). Cox proportional-hazard analysis, with the cohort as a major predictor variable, was performed to estimate relative risks for total mortality and for CVD (SAS statistical software, version 8.2, PHREG procedure; SAS Institute, Cary, NC, USA). We examined time dependence and interactions of the cohort with the other predictor variables. The results were compared to those obtained by logistic regression modelling.

Results

Comparing the two working groups, there was a secular decrease in blood pressure, and in the proportion of smokers, as well as an increase in BMI and in the proportion of those with treated diabetes mellitus (Table 1). On the other hand, the mean cholesterol values were higher in the CORDIS cohort.

Over the 11-year follow-up period, of the 881 death in the IIHD cohort 357 were due to CVD (40.5%), compared to 77 of 205 deaths (37.6%) in the CORDIS cohort. After adjustment for age, the hazard ratio for mortality for men in the IIHD cohort as compared to the CORDIS was 1.31 (95% CI: 1.12, 1.52) for total and 1.47 (95% CI: 1.16, 1.87) for CVD.

Adding SBP to the model, the hazard ratio (IIHD cohort compared to the CORDIS) for total mortality decreased to 1.09 (Table 2). It should be emphasized that after adjusting for age and leisure physical activity in both smokers and nonsmokers, the addition of SBP to the model still decreased the cohort effect significantly. Adding leisure physical activity or current smoking to the model did not decrease the hazard ratio (IIHD compared to the CORDIS) for all-cause mortality risk to the same extent. The same results were found for CVD mortality (Table 3).

Table 1 Differences in demographic and risk marker variables in two cohorts of Israeli workers with an inception date separated by 24 years (adjusted for age)

Variables	IIHD—1963 N=10 048 (mean (s.e.) or %)	CORDIS—1987 N=2237 (mean (s.e.) or %)	Difference	95% CI
Age (years)	51.7 (0.1)	49.2 (0.1)	2.5*	2.2, 2.8
SBP (mmHg)	140.3 (0.2)	131.7 (0.4)	−8.7*	−7.7, −9.6
DBP (mmHg)	84.7 (0.1)	80.6 (0.2)	−4.1*	−3.6, −4.7
Cholesterol (mg/dl)	209.7 (0.4)	217.6 (0.9)	7.9*	6.0, 9.8
BMI (kg/m ²)	25.67 (0.03)	26.39 (0.07)	0.72*	0.57, 0.88
BMI ≥27.8 kg/m ² (%)	24.54	30.96	6.4*	4.4, 8.5
Treated diabetes mellitus (%)	2.50	2.87	0.37	−0.36, 1.10
Smoking—current (%)	51.6	35.3	−16.3*	−14.0, −18.5
Regular physical activity (%)	9.9	19.1	9.2*	7.7, 10.6
BP ≥140/90 (%)	42.0	27.6	−14.4*	−16.5, −12.2
BP ≥160/95 (%)	21.2	12.4	−8.8*	−10.6, −7.0
Education ≥12 years (%)	38.6	31.8	−6.8*	−9.1, −4.6
≥1.5 persons/room (%)	68.1	36.6	−25.3*	−23.1, −27.4

SE=standard error, SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, BP=blood pressure, IIHD study=The Israeli Ischemic Heart Disease study, CORDIS study=Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) study. * $P<0.001$.

Table 2 Increased risk of total mortality in 1963–1973 (IIHD) compared to 1987–1997 (CORDIS) after the addition of various predictor variables to the Cox proportional hazards model

Variable	Total cohort hazard ratio	95% CI	Nonsmokers hazard ratio (95% CI)	95% CI
Age (years)	1.31	1.12, 1.52	1.41	1.15, 1.42
Age, SBP	1.09	0.94, 1.27	1.14	0.92, 1.40
Age, DBP	1.16	1.00, 1.35	1.22	0.99, 1.50
Age, leisure physical activity	1.29	1.11, 1.50	1.39	1.13, 1.70
Age, smoking	1.21	1.05, 1.42		
Age, SBP, physical activity	1.06	0.91, 1.24	1.12	0.91, 1.38

IIHD study=The Israeli Ischemic Heart Disease study, CORDIS study=Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) study, SBP=systolic blood pressure, DBP=diastolic blood pressure.

Table 3 Increased risk of CVD mortality in 1963–1973 (IIHD) compared to 1987–1997 (CORDIS) after the addition of various predictor variables to the Cox proportional hazards model

Variable	Total cohort hazard ratio	95% CI	Nonsmokers hazard ratio	95% CI
Age (years)	1.47	1.16, 1.87	1.77	1.26, 2.49
Age, SBP	1.18	0.88, 1.43	1.33	0.94, 1.88
Age, DBP	1.22	0.96, 1.56	1.43	1.02, 2.03
Age, smoking	1.37	1.07, 1.74		
Age, leisure activity	1.46	1.1, 1.86	1.76	1.25, 2.48
Age, SBP/leisure activity	1.11	0.87, 1.42	1.32	0.93, 1.87

IIHD study=The Israeli Ischemic Heart Disease study, CORDIS study=Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) study, SBP=systolic blood pressure, DBP=diastolic blood pressure.

The secular decrease in cardiovascular mortality was not homogeneous (Table 4). Mortality did not decline in smokers, and the secular effect was more pronounced in those with 12 years or more of formal education. Adding SBP to the model consistently decreased the association observed between study groups and total mortality.

The association of CVD mortality with SBP was similar in the two cohorts. In the CORDIS, we found

that for every 1 mmHg an increase of 2.1% (95% CI: 1.1, 3.2) of CVD mortality, and for the IIHD cohort the risk was 2.0% (95% CI: 1.7, 2.3) after adjustment for other risk factors (full models not shown).

The risk of dying from CVD in the IIHD was 47% greater than the CORDIS. Adjusting for SBP, the risk decreased to 18%, ‘explaining’ 61.7% ((47–18)/47) of the observed increased hazard of CVD mortality in the IIHD. After prior adjustment for leisure physical

Table 4 Increased risk of cardiovascular disease mortality in 1963–1973 (IIHD) compared to 1987–1997 (CORDIS) before and after adding SBP to the Cox proportional-hazard analysis (adjusted for age)

	Risk ratio	95% CI	P for trend	Risk ratio adjusted for SBP	95% CI	P for trend
Leisure activity			0.74			0.81
No	1.46	1.12, 1.89		1.11	0.85, 1.44	
Yes	1.53	0.80, 2.92		1.20	0.62, 2.35	
Birth place			0.84			0.75
Africa/Israel	1.61	1.06, 2.44		1.16	0.75, 1.78	
Asia/Europe	1.41	1.05, 1.91		1.09	0.81, 1.47	
Persons per room			0.61			0.80
<1.5	1.58	1.19, 2.09		1.18	0.88, 1.57	
≥1.5	1.40	0.85, 2.31		1.13	0.68, 1.86	
Age (years)			0.26			0.20
≤50	2.16	1.05, 4.45		1.56	0.75, 3.24	
>50	1.36	1.06, 1.76		1.06	0.82, 1.38	
Cholesterol (mg/dl)			0.70			0.99
<240	1.62	1.16, 2.25		1.23	0.88, 1.72	
≥240	1.61	1.11, 2.34		1.29	0.88, 1.88	
BMI (kg/m ²)			0.95			0.88
<27.8	1.50	1.11, 2.03		1.12	0.82, 1.52	
≥27.8	1.45	0.96, 2.18		1.12	0.74, 1.69	
Current smoking			0.02			0.03
No	1.77	1.26, 2.49		1.33	0.94, 1.88	
Yes	1.00	0.71, 1.40		0.77	0.54, 1.08	
Education			0.02			0.04
<12 years	1.22	0.92, 1.61		0.96	0.72, 1.28	
≥12 years	2.32	1.08, 3.82		1.66	1.00, 2.76	
Education <12 years			0.001			0.003
Smoking	0.80	0.54, 1.19		0.66	0.44, 0.98	
Nonsmoking	1.55	1.04, 2.32		1.17	0.77, 1.76	
Education ≥12 years						
Smoking	1.60	0.78, 3.29		1.07	0.52, 2.23	
Nonsmoking	2.62	1.31, 5.23		2.03	1.00, 4.10	

IIHD study=The Israeli Ischemic Heart Disease study, CORDIS study=Cardiovascular Occupational Risk Factor Determination in Israeli Industry (CORDIS) study, SBP=systolic blood pressure, BMI=body mass index.

activity, in nonsmokers the 23% decreased risk after adding SBP to the model ‘explained’ 79% (29/6/29), and in smokers the 27% decreased risk ‘explained’ 69.2% (39/12/39) of the observed increased hazard of CVD mortality in the IIHD. In a logistic regression model, the risk was 48% greater in the IIHD than in the CORDIS. After adding SBP, the risk decreased to 12%, ‘explaining’ 75% ((48–12)/48) of the observed increased risk of dying from CVD.

Of the 2224 men in CORDIS, there were 645 patients (29.0%) with blood pressures of 140/90 or greater, 258 were treated (40.0% of those with elevated blood pressure). Of those treated, 123 had blood pressures under the 140/90 mark (47.7% of those treated). Assuming an average 20 mmHg decrease in SBP in those treated, we can calculate that 26.7% of the secular decrease in SBP was due to hypertensive drug therapy (258 treated × 20 mmHg/2224 total men × 8.7 mmHg–average decrease).

Discussion

We found that over half of the decrease in CVD mortality was explained by the 8.7 mmHg secular difference decrease in mean SBP between the two study cohorts, a consistent finding over the various

subgroups. We are unaware of other similar studies using a single model to study secular changes in CVD mortality in cohorts with various inception dates. Finnish investigators did use a single model to study secular changes in mortality from stroke in general population cohorts recruited between 1972 and 1992. They found that a fall of 5 mm of diastolic blood pressure was the major factor in explaining the 66% decrease in stroke mortality observed over that period.¹⁸ The decrease in the prevalence of smoking and the decrease in cholesterol had only a minor association with the decline in stroke mortality.

On the other hand, studies using models that incorporate changes in risk factors and improvements in medical therapy have estimated only a modest effect of secular changes in blood pressure.^{5,18} Capewell *et al* estimated that the treatment of hypertension was responsible for only 7%, and secular population blood pressure changes for 8% of the 23.6% nationwide decrease in CHD mortality rates between 1982 and 1993.¹⁸ Hunink *et al*⁵ attempted to predict the decline in CHD mortality occurring in the US from 1980 to 1990. They were able to predict nearly all of the 35% observed decreased risk of acute coronary mortality and estimated that the effect of decreasing DBP ex-

plained only 14% of the total. The major problem with these models is that they use benefits estimated from interventional studies carried out in tertiary centres probably overestimating actual benefit in the community. Furthermore, it is possible that there is an interaction between lower blood pressures in the population and improved outcomes in patients who become ill and are treated with modern coronary care.¹⁹

Possible limitations

Our results could have been biased by a differential healthy worker effect, but the 1.31 age-adjusted differential risk in total mortality, found in the IIHD compared to the CORDIS, is nearly identical to that observed in the general population of Jewish men over the same time period.²⁰ External validity might also be questioned, but is supported by similar secular changes in risk factors and cardiovascular mortality^{3,4,18,21} observed in other developed countries. The decrease in SBP of around 8–12 mmHg reported in both the United States and Europe^{6–8} is comparable to the 8.7 mmHg observed in our study during a similar time period. The increased incremental risk of CVD mortality of around 2.0% per mmHg in both cohorts after adjustment for the other risk factors is consistent with the incremental risk of death due to CVD of 2–4% for every increase of 1 mmHg of SBP, reported in other developed countries.^{9–12} Finally, the Seven Country study⁹ found as we did that the incremental risk of SBP for coronary heart disease has not changed over time.

The reasons for the secular decrease in blood pressure are not entirely understood. Certainly, one major factor is an increase in the prevalence of pharmacological treatment of hypertension. In the CORDIS, 40% of patients with hypertension were treated, and of those treated, 46.5% had blood pressures under the 140/90 mark. This degree of treatment is similar to that reported in the NHANES III²² and the proportion controlled similar to both the NHANES III and results recently reported for hypertensive men, treated by the Department of Veterans Affairs' clinics.²³ However, the drug treatment in the CORDIS, which was not used in the IIHD cohort, explained only 26.7% of the secular decrease in SBP even after optimistically assuming that such treatment resulted in an average 20 mmHg decrease in SBP.²⁴ The increase in BMI should have acted to increase rather than decrease SBP values, and it is possible that the secular change would have been even greater, had the BMI remained constant. It has been suggested that a decrease in saturated oil and increasing polyunsaturated fats in the diet might explain some of the secular changes in blood pressure,²⁵ but in Israel there has actually been an increase in both fat consumption from animals and other sources over the last 30 years,²⁶ suggesting that

changes in fat consumption did not play a major role in the secular change in SBP in Israel.

We cannot rule out that the different methodologies led to the differences in measured blood pressures between the two cohorts. Physicians measured blood pressures in the IIHD, whereas technicians measured blood pressures in the CORDIS. Still, the blood pressure equipment, patient position and time of test were similar in the two studies. Digital bias towards 0 values was observed in 40% of the measurements in both studies, similar to results reported in the early NHANES surveys.⁸ We used the first blood pressure measurement because the methodology was the same in both the studies. However, if an average of the three blood pressure measurements was used instead of the first blood pressure measurement, the results were nearly identical (not shown).

The lack of a secular advantage in smokers and in those with a low educational status is consistent with studies showing that there are discordant secular changes around the world. There is an emerging epidemic of CVD in developing countries, where an increase in the standard of living has not yet been realized.^{27,28} The epidemic is probably not distributed equally among the various segments of the population. In Czechoslovakia, death rates increased from 1980–1981 to 1995 in those with a limited elementary education, but not in the more educated.²⁸

We conclude that declining blood pressure values are a major factor in explaining the secular decrease in CVD over a period of 24 years in Israel. Drug treatment for hypertension explains part of this trend emphasizing the importance of continued efforts to control blood pressure in the general population. This perhaps should be our number one priority for public health intervention in adults.

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