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Methodological Issues for a Large-Scale Intervention Trial of Lifestyle Modification: Interim Assessment of the High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study

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Abstract

Objective: To clarify the methodological issues for the High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP study), which is a 4-year non-randomized control trial, an interim assessment of male participants was performed 3 years after the baseline survey.

Methods: We had approximately 2,500 and 4,000 participants in the intervention and control groups, respectively. The population measures and prevalence of risk factors at each year, and between the baseline and 4th examinations were compared between the two groups. The personal trends of returning participants who were in the study at the 1st and 4th examinations were also evaluated.

Results: During the 3 years, an increase in serum HDL cholesterol (2.7 mg/dl), and a reduction in the prevalence of hypertriglycemia detected with fasting blood samples (3.6%) and current smokers (5.4%) were observed in the intervention group. The mean HDL cholesterol level was significantly higher in the intervention group than in the control group at the 4th examination, reversed from the baseline survey. The serum non-HDL cholesterol level was significantly increased only in the control group. There was also a significant increase in the prevalence of hypertriglycemia and high plasma glucose detected with fasting blood samples in the control group. The return participation rate after 3 years was 72.2% for the intervention group and 74.9% for the control group. The above-mentioned changes for risk factors were mainly due to returning participants at each examination.

Conclusion: These interventional methods may be effective in improving overall cardiovascular risk factors in the population. However, the low return participation rate will dilute the effect of the intervention.

Key words: population strategy, intervention, interim assessment, return participation, cardiovascular risk factor

Introduction

Many intervention studies have shown successful results by clear improvements in cardiovascular risk factors (1–6). However, the majority of these studies targeted high-risk subjects who had at least moderate levels of cardiovascular risk factors. Because a high-risk strategy does not have a sufficient influence on subjects with low latent risk, it may not significantly reduce overall cardiovascular risk in the population. To effectively reduce a specific disease in a population, it is beneficial to shift the distribution of its risk factors towards the low-risk side (7). For example, a mean reduction in systolic blood pressure (SBP) of 2.2 mmHg in middle-aged subjects was

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associated with a 4% reduction in the risk of coronary death and a 6% lower risk of stroke death (8). These findings demonstrate that such population-based strategies involving intervention in a large number of low-risk subjects are effective in reducing risk in the whole population.

There have been a number of trials using a population strategy in Western populations (9–14). However, there have been few studies promoting a population strategy in Japan, except in some local municipalities (15,16). Accordingly, in 1998 we initiated the High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP study), which incorporated a program with combined population and high-risk strategies for improving cardiovascular risk factors in workplaces (17–19). In this report, the results of an interim assessment of this intervention trial for male participants are described, and the methodological issues related to a large-scale intervention trial in worksite populations are discussed.

Methods

Study population

The details of this non-randomized control trial have been described elsewhere (17–19). Briefly, employee groups from 12 companies were divided into an intervention group (6 companies: A-F), in which the environment was improved based on a population strategy in addition to individual intervention (high-risk strategy), and a control group (6 companies: H-L) that was provided with only the individual intervention teaching material. We had 2,515 and 3,289 participants in the intervention and control groups, respectively, at the baseline survey conducted in 1999-2000. After the baseline survey, approximately 6,500 (2,500 for the intervention group and 4,000 for the control group) employees participated in this study every year.

Company A was the head office of a life insurance company, Companies D and H were factories of chemical companies, Company L was a research laboratory of an electrical appliance manufacturer, and the other eight companies were factories of electrical appliance manufacturers. The details of the intervention methods have been previously reported elsewhere (18,19). The population strategy for health promotion consists of 3 fields, i.e., nutrition, physical activity, and smoking. In each field, a researcher's working team was organized and has been handling intervention for its field. These interventions are planned to be performed in 6 monthly cycles over 4 years. As a high-risk strategy, individual health education programs of 6 months were provided for any participants with high-normal or greater blood pressure levels, hypercholesterolemia, or high plasma glucose.

Informed consent was obtained from the participants regarding individual guidance for the high-risk strategy. The safety hygiene committee in each company examined the plan and ethical problems in the population strategy every month. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for Ethical Issues (No. 10–16).

Data collection and standardization

Biological data were collected at the time of annual health check-ups. A spot urine sample for every participant was also collected for determination of daily sodium and potassium excretion (20). Blood pressure was measured in duplicate after the participants had rested for 5 minutes using the same newly calibrated automatic sphygmomanometer at each company (Nippon Colin, BP-103iII), with the mean value being used in the analyses. For the measurement of lipids, general laboratories to which blood examination was entrusted by each company were standardized through the US Cholesterol Reference Method Laboratory Network (CRMLN) controlled by the CDC (Centers for Disease Control and Prevention, Atlanta) (21).

We did not use mean values of LDL (low-density lipoprotein) cholesterol, serum triglyceride or plasma glucose because about one-third of the participants did not have their fasting blood samples collected. Accordingly, we used the mean level of non-HDL (high-density lipoprotein) cholesterol (serum total cholesterol–serum HDL cholesterol), or the prevalence of hypertriglycemia and high plasma glucose as assessment variables. Hypertriglycemia was defined as a fasting serum triglyceride of 150 mg/dl (1.69 mmol/L) or higher, or a non-fasting serum triglyceride of 200 mg/dl (2.26 mmol/L) or higher, and high plasma glucose was defined as a fasting plasma glucose of 110 mg/dl (6.11 mmol/L) or higher, or a non-fasting plasma glucose of 120 mg/dl (6.66 mmol/L) or higher. "Fasting" was defined as at least 8 hours passing since the subject's previous meal. Evaluation of smoking habits was carried out using a standardized questionnaire produced by the researchers.

Statistical analysis

In this study, we performed an interim assessment of this intervention trial. The trends for main cardiovascular risk factors during the 3 years after the baseline survey were analyzed. For comparison of risk factors between the intervention and the control group at each year, and for population differences between baseline characteristics and findings after 3 years, unpaired t-tests or chi-square tests were used. We defined a person who participated in both the 1st and 4th examinations as a returning participant. The changes in returning participants between the 1st and 4th examinations were analyzed by paired t-tests or McNemar tests. Concerning the comparison of returning participant change for the prevalence of each risk factor between the two groups, Mann-Whitney U tests were used after we defined the change into three categories: getting worse=1, no change=2, improving=3.

The Statistical Package for Social Sciences (SPSS Japan Inc. version 11.0J, Tokyo, Japan) was used for the analyses. All probability values were two-tailed and all statistical tests were considered to be significant with a probability value of less than 0.05.

Results

Table 1 shows the risk characteristics between the intervention group and the control group during the 3 years. No difference was observed between the two groups in age, SBP, diastolic blood pressure (DBP), body mass index (BMI) or the prevalence of current smokers in the 1st examination (baseline survey). However, the intervention group had higher non-HDL

Table 1 Trend for major risk characteristics in the surveyed population during 3 years, males

Risk characteristics	Group	1st examination (baseline)				2nd examination (after 1 year)				3rd examination (after 2 years)				4th examination (after 3 years)				P-value between 1st and 4th examinations
		N	Mean or Prevalence	SD	P-value between two groups	N	Mean or Prevalence	SD	P-value between two groups	N	Mean or Prevalence	SD	P-value between two groups	N	Mean or Prevalence	SD	P-value between two groups	
Age, years	Intervention	2,515	39.4	10.1	0.439	2,493	40.1	10.0	0.137	2,465	39.8	9.9	0.644	2,413	40.4	9.4	0.747	0.001
	Control	3,289	39.6	9.4		4,218	39.7	9.9		4,024	39.7	9.7		3,960	40.3	9.5		0.002
Systolic blood pressure, mmHg	Intervention	2,512	119.0	16.5	0.601	2,436	119.0	16.4	0.829	2,400	120.1	16.1	0.019	2,292	119.5	16.2	0.166	0.290
	Control	3,193	118.8	15.2		4,163	118.9	15.6		3,985	119.1	15.4		3,890	119.0	15.6		0.693
Diastolic blood pressure, mmHg	Intervention	2,512	72.5	11.4	0.180	2,436	72.7	11.6	0.729	2,400	73.8	11.5	0.034	2,292	73.5	11.7	0.002	0.002
	Control	3,193	72.9	11.1		4,163	72.8	11.5		3,985	73.2	11.4		3,890	72.6	11.6		0.215
Non-HDL cholesterol †, mg/dl	Intervention	1,589	145.7	35.2	<0.001	1,830	145.3	36.2	<0.001	1,629	147.7	36.8	<0.001	1,633	145.4	36.6	0.030	0.814
	Control	2,642	139.2	35.9		3,396	139.6	36.4		3,247	142.4	35.7		3,184	143.0	35.7		<0.001
HDL cholesterol, mg/dl	Intervention	1,589	54.1	14.4	<0.001	1,830	54.6	14.3	<0.001	1,629	55.1	14.2	0.579	1,633	56.8	14.5	0.009	<0.001
	Control	2,642	56.1	13.1		3,396	56.8	13.4		3,247	54.9	13.3		3,184	55.7	13.6		0.251
Hypertriglycemia (fasting) ‡, %	Intervention	1,150	24.4		<0.001	1,340	24.4		0.909	1,034	24.6		0.212	1,089	20.8		0.542	0.044
	Control	2,420	18.6			3,053	24.6			2,827	22.6			2,763	21.7			0.002
Hypertriglycemia (non-fasting) ‡, %	Intervention	435	29.2		0.017	452	29.6		<0.001	569	27.1		0.021	502	29.3		<0.001	0.948
	Control	66	15.2			320	17.8			377	20.4			250	13.6			1.000
High plasma glucose (fasting) ¶, %	Intervention	1,150	13.7		<0.001	1,355	13.3		<0.001	1,034	16.0		<0.001	1,089	13.8		0.017	0.953
	Control	2,420	7.4			3,050	7.8			2,823	11.0			2,763	11.0			<0.001
High plasma glucose (non-fasting) ¶, %	Intervention	435	20.2		<0.001	450	19.3		<0.001	570	15.3		0.001	502	16.5		<0.001	0.234
	Control	66	3.0			185	2.7			273	7.0			250	4.0			1.000
Body mass index, kg/m^2	Intervention	2,514	23.0	3.1	0.106	2,478	23.0	3.1	0.022	2,463	23.2	3.2	0.871	2,347	23.3	3.2	0.850	0.001
	Control	3,292	23.1	3.0		4,217	23.2	3.1		4,023	23.2	3.1		3,955	23.3	3.1		0.026
Urinary salt excretion, g/day	Intervention	2,376	9.4	2.2	<0.001		§			2,410	9.3	2.2	0.001	2,250	9.3	2.2	<0.001	0.046
	Control	3,256	9.0	2.2			§			3,087	9.1	2.2		2,991	9.0	2.2		0.709
Current smokers, %	Intervention	2,362	55.0		0.173	2,339	52.7		0.979	2,374	51.8		0.391	2,280	49.6		0.578	<0.001
	Control	3,171	53.1			3,957	52.7			3,926	50.7			3,642	48.8			<0.001

P values were calculated by unpaired t tests or chi square tests. SD means standard deviation.
† Non-HDL cholesterol was calculated as follows: total cholesterol - HDL cholesterol. HDL means "High-density lipoprotein".
‡ Hypertriglycemia was defined as fasting serum triglyceride>=150 mg/dl (1.69 mmol/L) or non-fasting serum triglyceride>=200 mg/dl (2.26 mmol/L).
¶ High plasma glucose was defined as fasting plasma glucose>=110 mg/dl (6.11 mmol/L) or non-fasting plasma glucose>=120 mg/dl (6.66 mmol/L).
§ Urinary salt excretion was not measured in this year.

Table 2 Number of participants at the 4th examination who had participated in the baseline survey, males

Companies	Number of participants at the 1st examination, baseline survey (A)	Number of participants at the 4th examination who had participated in the 1st examination (B)	B*100/A (%)
A †	402	206	51.2
B	622	521	83.8
C	481	336	69.9
D	494	317	64.2
E	233	186	79.8
F	283	250	88.3
Intervention Group	2,515	1,816	72.2
G	964	809	83.9
H	509	419	82.3
I	337	297	88.1
J	336	287	85.4
K	674	444	65.9
L †	462	203	43.9
Control Group	3,282	2,459	74.9
Total	5,797	4,275	73.7

† Non-factory population.

cholesterol levels and urinary sodium excretion, lower HDL cholesterol levels, and a higher prevalence of participants with hypertriglycemia or high plasma glucose, compared with the control group. These differences between the two groups were not substantially changed in the 2nd examination. In the 3rd examination, the difference in HDL cholesterol between the two groups was not significantly different, whilst the intervention group had higher SBP and DBP. In the 4th examination, the

Table 3 Trends for blood pressure, cholesterol, BMI and urinary salt excretion in the returning participants during 3 years, males

Risk characteristics	Group	N	1st examination (baseline)	SD	4th examination (after 3 years)	SD	change	SD	P-value † between 1st and 4th examinations	P-value ‡ between two groups
Age, years	Intervention	1,816	37.5	9.2	41.0	9.2	3.5	0.34	<0.001	0.994
	Control	2,470	38.1	8.8	41.6	8.8	3.5	0.28	<0.001	
Systolic blood pressure, mmHg	Intervention	1,728	118.7	16.4	120.2	16.5	1.5	11.4	<0.001	<0.001
	Control	2,367	118.9	15.1	118.9	15.8	0	11.4	0.957	
Diastolic blood pressure, mmHg	Intervention	1,728	71.8	11.1	74.2	11.8	2.4	7.68	<0.001	<0.001
	Control	2,367	72.7	11.0	73.1	11.6	0.4	7.89	0.012	
Non-HDL cholesterol, mg/dl	Intervention	957	145.5	35.7	147.2	36.4	1.7	24.3	0.031	<0.001
	Control	1,857	138.4	35.9	143.6	36.1	5.2	23.2	<0.001	
HDL cholesterol, mg/dl	Intervention	957	54.3	14.6	56.5	15.0	2.2	8.70	<0.001	<0.001
	Control	1,857	56.0	12.9	56.1	13.6	0.1	7.71	0.406	
Body mass index, kg/m2	Intervention	1,750	22.8	3.1	23.2	3.2	0.4	1.13	<0.001	<0.001
	Control	2,470	23.1	2.9	23.3	3.0	0.2	1.08	<0.001	
Urinary salt excretion, g/day	Intervention	1,619	9.3	2.2	9.3	2.2	0	2.58	0.894	0.638
	Control	2,420	9.1	2.2	9.1	2.2	0	2.50	0.559	

Non-HDL cholesterol was defined as in Table 1.
† P values were calculated by paired t tests.
‡ P values were calculated by unpaired t tests.

Table 4 Trends in the prevalence (%) of hypertriglycemia, high plasma glucose and current smokers in the returning participants during 3 years, males

Risk characteristics	Group	N	1st examination (baseline)	4th examination (after 3 years)	change	P-value between 1st and 4th examinations †	P-value ‡ between two groups
Hypertriglycemia (fasting), %	Intervention	601	24.1	22.5	−1.6	0.337	0.139
	Control	1,579	19.6	20.9	1.3	0.247	
	P-values ¶		0.021	0.447			
Hypertriglycemia (non-fasting), %	Intervention	199	35.7	41.2	5.5	0.178	0.353
	Control	8	25.0	12.5	−12.5	1.000	
	P-values ¶		0.715	0.148			
High plasma glucose (fasting), %	Intervention	601	11.5	16.0	4.5	0.001	0.909
	Control	1,579	6.8	11.6	4.8	<0.001	
	P-values ¶		0.001	0.008			
High plasma glucose (non-fasting), %	Intervention	199	27.6	27.6	0.0	1.000	1.000
	Control	8	12.5	12.5	0.0	1.000	
	P-values ¶		0.686	0.686			
Current smokers, %	Intervention	1,683	56.5	51.3	−5.2	<0.001	0.035
	Control	2,317	54.1	50.7	−3.4	<0.001	
	P-values ¶		0.130	0.701			

Hypertriglycemia and high plasma glucose were defined as in Table 1.
† P values were calculated by McNemar tests.
‡ P values were calculated by Mann-Whitney U tests.
¶ P values between two groups were calculated by chi square tests.

intervention group had higher DBP and HDL cholesterol levels than those of the control group, and the difference in the prevalence of hypertriglycemia detected with fasting blood samples between the two groups was not significant.

Comparing results between the 1st and 4th examinations in the intervention group, there was a significant increase in age, DBP, HDL cholesterol and BMI, and a significant decrease in urinary salt excretion level and the prevalence of hypertriglycemia detected with fasting blood samples and current smokers. In the control group, there was a significant increase in age, DBP, non-HDL cholesterol and BMI level and the prevalence of hypertriglycemia and high plasma glucose detected with fasting serum samples, and a significant decrease in the prevalence of current smokers. The prevalence of participants who were taking anti-hypertensive, lipid-lowering and anti-diabetic medicines was relatively low in this population, at 3.6%, 2.1% and

0.9% in the intervention group and 3.4%, 1.8% and 1.1% in the control group at the 1st examination, respectively. There was no significant difference between the two groups. At the 4th examination, the prevalence was 4.6%, 2.5%, 0.9% in the intervention group, and 4.5%, 2.0% and 1.6% in the control group, respectively. There was a significant difference only in the prevalence of anti-diabetic users, which was lower in the intervention group than in the control group (data not shown in the table).

Table 2 indicates the number of participants at the 4th examination who had participated in the baseline survey. The return participation rate was 72.2% for the intervention group and 74.9% for the control group (χ^2=5.43, P=0.02). The return participation rate of the two non-factory populations (Companies A and L) was much lower than that in the other companies.

The trends of the participants at the baseline survey for SBP and DBP, non-HDL cholesterol, HDL cholesterol, BMI and urinary salt excretion between the 1st and 4th examinations (3 years) are shown in Table 3. The trends were similar to those of the population trends shown in Table 1. The 3-year increase in SBP or DBP, HDL cholesterol and BMI was greater in the intervention group than in the control group, whilst the 3-year increase in non-HDL cholesterol was lower in the intervention group than that in the control group. There was no difference in the urinary salt excretion trend between the two groups.

The trends of the participants at the baseline survey for the prevalence of hypertriglycemia, high plasma glucose and current smokers are shown in Table 4. For both groups, the prevalence of current smokers was significantly decreased, and the prevalence of fasting high plasma glucose was significantly increased. There was no significant change in the prevalence of hypertriglycemia either in the intervention or the control group. The significant difference between the two groups observed in the prevalence of hypertriglycemia detected with fasting blood samples from the baseline survey disappeared at the 4th examination. The 3-year decrease in the prevalence of current smokers was significantly greater in the intervention group compared to that in the control group.

Discussion

In the interim assessment of the HIPOP-OHP study, we showed a population improvement in the serum level of HDL cholesterol, urinary salt excretion, and the prevalence of current smokers and hypertriglycemia. Furthermore, the serum levels of non-HDL cholesterol and the prevalence of hypertriglycemia and high plasma glucose detected with fasting blood samples in the intervention group did not increase, whilst they significantly increased in the control group. These changes were mainly due to serial examinations of returning participants during the 3 years. However, the average DBP increased in the intervention group, whilst it did not change in the control group. The 3-year increases in SBP and DBP in the returning participants were also higher in the intervention group than those in the control group.

We have already reported that the intervention group had a significantly higher risk of cardiovascular disease, especially due to dyslipidemia and high plasma glucose, than the control group at the baseline survey because of a non-randomized design (18). Furthermore, although there were no differences between the two groups in SBP and DBP averages at the baseline survey, the urinary salt excretion for the intervention group was significantly higher than that of the control group (18).

Accordingly, we have been focused on the improvement of dyslipidemia, high plasma glucose and urinary salt excretion in the first half of our intervention. Generally speaking, cardiovascular risk factors deteriorated year by year due to aging. However, concerning the lipid factors, the average level of HDL cholesterol in the intervention group was significantly increased and the average level of non-HDL cholesterol remained nearly stable, whilst both of these factors in the control group deteriorated. Furthermore, the prevalence of hypertriglycemia detected with fasting blood samples in the intervention group was decreased in the returning participants, although the statistical analysis did not reach a significant level, whilst it was increased in the control group. Thus, we seemed to achieve some success in improvement, or at least lack of deterioration, for the above-mentioned risk factors.

The INTERSALT study suggested that urinary sodium excretion would be associated with increased blood pressure in the future (22). Therefore, the difference in the change in blood pressure between the two groups might be partially affected by the initial difference in urinary salt excretion, which was nearly equivalent to that of dietary salt intake. We are going to devote additional and continuous effort to reducing salt intake in the intervention period until the end of this study. Furthermore, effective strategies to decrease or at least maintain the mean blood pressure level are necessary in the intervention group.

There have been some health promotion trials employing a population strategy, especially in Western populations (9–15). Several of these have shown the difficulty of inducing individuals to change their behaviour by only providing information about a healthy lifestyle (11–13). In the British population of a European collaborative trial for the multifactorial prevention of coronary heart disease that included both high-risk and population strategies, Rose et al. reported a disappointingly low response to mass advice using posters, evening meetings, film showings and question–and-answer sessions (23). Because we have also been facing this same problem in the present study, in addition to mass advice, we have also attempted to make specific environmental changes such as decreasing sodium content in the food of the company dining rooms and constructing pathways or making maps for walking in the workplaces. However, the effects of environmental change in the intervention group were considered limited, for example, because one company had no dining room in the workplace (Company F), another had only a few customers at their dining room in the workplace (Company E), and we were able to construct a walking pathway in the factory only for Company B. Therefore, the main effects of our intervention study are being influenced strongly by the personal response to the information presented by mass advice. Thus, this study remains important in that effective methods are being developed for presenting information to induce individuals to change their behaviour.

The main limitation of the present study is the influence of periodic or non-periodic personnel changes in the participating companies. The population at the end of this study will not be

the same as that at the baseline examination. During the 3 years, about 30% of the participants were moved from their worksites. This rate will increase at the endpoint of this study. These personnel changes were not due only to retirement. A few years ago, most Japanese employees were hired for a permanent job and retired at the age of 60. However, due to the recent long recession in the Japanese economy, lay-offs of employees before retirement age or company mergers have frequently occurred in Japanese companies. In our study population, Company C was merged with another company during the 3 years, and there were unexpected rates of lay-offs in the other companies. When we excluded participants at the baseline survey who were aged 57 years or older and would have reached the retirement age of 60 at the 4th examination, the return participation rate at the 4th examination was not substantially affected (75.3% for the intervention group and 77.0% for the control group). These return participation rates were much lower than those expected before the commencement of this trial.

However, the HIPOP-OHP study involved many researchers cooperating with the staff in each company with the aim of improving cardiovascular risk factors based on high-risk and population strategies (18), and, at present, intervention is being conducted in the intervention group. It is anticipated that the protocol developed in this study will contribute greatly to occupational health promotion in Japan.

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Appendix

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