表.6 肥満および危険因子の集積と医療費との関連(危険因子に喫煙を含める)

(滋賀県26市町)

分類	肥満	性別	危険因子	対象者数(人)	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額(円)	過剰医療費割合(%)	保健指導後の有病率(%)	改善後過剰医療費(%)	保健指導での改善が必要な対象者数(人)	期待される医療費減少割合(%)
入院医療費	なし	男性	0	730	20,249	86,778	0	1,134,248							
			1	2,321	22,243	91,690	0	1,790,077	1.10	1,994	1.6	50	0.8		
			2以上	4,471	33,793	162,057	0	6,459,716	1.67	13,544	21.5	50	10.8		
		女性	0	3,796	8,953	59,073	0	1,990,019							
			1	5,610	18,292	135,499	0	4,902,264	2.04	9,339	17.1	50	8.5		
			2以上	4,385	21,493	112,734	0	3,282,960	2.40	12,540	17.9	50	9.0		
	あり	男性	0	116	14,381	63,670	0	465,640	0.71	0					
			1	493	25,577	97,122	0	1,045,511	1.26	5,328	0.9	50	0.5		
			2以上	1,756	28,112	169,218	0	5,549,420	1.39	7,863	4.9	50	2.5		
		女性	0	464	7,323	39,175	0	490,971	0.82	0					
			1	1,510	19,787	93,050	0	1,382,756	2.21	10,834	5.3	50	2.7		
			2以上	2,285	18,566	107,343	0	3,768,690	2.07	9,613	7.2	50	3.6		
入院外医療費	なし	男性	0	730	24,928	33,082	0	371,770							
			1	2,321	29,923	68,478	0	2,382,775	1.20	4,995	3.8	50	1.9		
			2以上	4,471	31,967	52,960	0	1,727,330	1.28	7,039	10.4	50	5.2		
		女性	0	3,796	18,979	27,861	0	683,618							
			1	5,610	25,722	59,392	0	3,811,622	1.36	6,743	7.7	50	3.8		
			2以上	4,385	32,291	56,054	0	2,746,193	1.70	13,312	11.9	50	5.9		
	あり	男性	0	116	21,696	24,024	0	119,417	0.87	0					
			1	493	30,460	37,515	0	398,895	1.22	5,532	0.9	50	0.5		
			2以上	1,756	30,393	40,962	0	745,322	1.22	5,465	3.2	50	1.6		
		女性	0	464	21,171	33,996	0	419,929	1.12	2,193					
			1	1,510	30,023	34,135	0	640,892	1.58	11,044	3.4	50	1.7		
			2以上	2,285	34,545	37,096	0	507,074	1.82	15,567	7.2	50	3.6		
入院外医療費+保険調剤費	なし	男性	0	730	27,263	90,795	0	1,188,352	−						
			1	2,321	30,346	96,914	0	1,829,187	1.11	3,083	2.0	50	1.0		
			2以上	4,471	42,351	164,214	0	6,459,716	1.55	15,088	18.5	50	9.3		
		女性	0	3,796	14,092	61,343	0	1,994,015	−						
			1	5,610	25,816	138,046	0	5,003,316	1.83	11,724	14.7	50	7.3		
			2以上	4,385	30,769	115,356	0	3,284,960	2.18	16,677	16.3	50	8.2		
	あり	男性	0	116	19,108	65,049	0	465,640	0.70	0					
			1	493	36,054	115,560	0	1,679,890	1.32	8,790	1.2	50	0.6		
			2以上	1,756	36,854	170,799	0	5,551,494	1.35	9,591	4.6	50	2.3		
		女性	0	464	13,893	44,209	0	490,971	0.99	0					
			1	1,510	28,179	95,415	0	1,382,756	2.00	14,088	4.8	50	2.4		
			2以上	2,285	28,706	109,705	0	3,768,690	2.04	14,614	7.5	50	3.7		
医療費総額	なし	男性	0	730	52,191	107,268	0	1,272,981	−						
			1	2,321	60,269	130,339	0	2,382,775	1.15	8,077	2.8	50	1.4		
			2以上	4,471	74,318	179,445	0	6,529,652	1.42	22,127	14.9	50	7.4		
		女性	0	3,796	33,070	72,388	0	2,049,250	−						
			1	5,610	51,537	157,891	0	5,152,460	1.56	18,467	11.0	50	5.5		
			2以上	4,385	63,060	138,494	0	3,801,887	1.91	29,989	14.0	50	7.0		
	あり	男性	0	116	40,804	75,718	0	544,343	0.78	0					
			1	493	66,514	131,342	0	1,799,157	1.27	14,323	1.1	85	0.9	73.95	0.2
			2以上	1,756	67,247	185,453	0	5,873,738	1.29	15,056	4.0	60	2.4	702.4	1.6
		女性	0	464	35,064	59,660	0	557,075	1.06	1,994					
			1	1,510	58,202	107,641	0	1,452,821	1.76	25,132	4.0	85	3.4	226.5	0.6
			2以上	2,285	63,251	121,321	0	3,814,162	1.91	30,181	7.3	60	4.4	914	2.9
保健指導での改善が必要な対象者数	肥満者			6,624	人中									1917	人
その肥満者に占める割合														29	%
期待される医療費減少割合(%)		男性													1.7
		女性													3.5

注意：医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が1未満のときは計算せず、0とした。

表 7 肥満および危険因子の集積と医療費との関連（危険因子に喫煙を含めない）

（滋賀県26市町）

分類	肥満	性別	危険因子	対象者数（人）	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額（円）	過剰医療費割合（%）	保健指導後の有病率（%）	改善後過剰医療費（%）	保健指導での改善が必要な対象者数（人）	期待される医療費減少割合（%）
入院医療費	なし	男性	0	2,096	16,575	71,914	0	1,134,248							
			1	4,800	22,551	93,897	0	1,790,077	1.36	5,976	7.0	50	3.5		
			2以上	5,480	31,795	148,158	0	6,459,716	1.92	15,220	20.4	50	10.2		
		女性	0	6,260	8,619	53,885	0	1,990,019							
			1	8,732	15,817	114,496	0	4,902,264	1.84	7,198	14.7	50	7.3		
			2以上	6,303	19,821	128,116	0	6,251,620	2.30	11,202	16.5	50	8.2		
	あり	男性	0	283	14,307	54,592	0	465,640	0.86	0					
			1	1,114	20,930	87,354	0	1,049,143	1.26	4,355	1.2	50	0.6		
			2以上	2,482	25,613	147,999	0	5,549,420	1.55	9,038	5.5	50	2.7		
		女性	0	758	15,307	176,314	0	4,651,002	1.78	6,688					
			1	2,418	17,068	86,742	0	1,382,756	1.98	8,449	4.8	50	2.4		
			2以上	3,350	17,434	97,762	0	3,768,690	2.02	8,815	6.9	50	3.4		
入院外医療費	なし	男性	0	2,096	22,575	61,271	0	2,382,775							
			1	4,800	26,415	39,901	0	1,184,998	1.17	3,840	3.9	50	2.0		
			2以上	5,480	33,061	53,961	0	1,727,330	1.46	10,486	12.2	50	6.1		
		女性	0	6,260	17,644	26,121	0	683,618							
			1	8,732	24,998	50,479	0	3,811,622	1.42	7,354	8.9	50	4.4		
			2以上	6,303	31,007	51,135	0	2,746,193	1.76	13,363	11.6	50	5.8		
	あり	男性	0	283	20,868	26,802	0	192,620	0.92	0					
			1	1,114	27,254	39,858	0	644,695	1.21	4,679	1.1	50	0.6		
			2以上	2,482	31,242	40,807	0	745,322	1.38	8,667	4.6	50	2.3		
		女性	0	758	22,799	93,291	0	2,451,741	1.29	5,155					
			1	2,418	29,083	32,720	0	640,892	1.65	11,439	3.8	50	1.9		
			2以上	3,350	33,552	35,617	0	507,074	1.90	15,908	7.4	50	3.7		
入院外医療費＋保険調剤費	なし	男性	0	2,096	22,576	74,989	0	1,188,352	−						
			1	4,800	29,936	97,978	0	1,829,187	1.33	7,360	6.6	50	3.3		
			2以上	5,480	40,404	150,624	0	6,459,716	1.79	17,828	18.3	50	9.1		
		女性	0	6,260	13,365	56,294	0	1,994,015	−						
			1	8,732	22,814	117,205	0	5,003,316	1.71	9,449	13.1	50	6.6		
			2以上	6,303	28,118	129,792	0	6,251,620	2.10	14,753	14.8	50	7.4		
	あり	男性	0	283	18,794	56,192	0	465,640	0.83	0					
			1	1,114	28,950	98,067	0	1,679,890	1.28	6,374	1.3	50	0.7		
			2以上	2,482	34,203	149,962	0	5,551,494	1.51	11,627	5.4	50	2.7		
		女性	0	758	22,213	203,178	0	5,399,536	1.66	8,848					
			1	2,418	24,945	88,883	0	1,382,756	1.87	11,581	4.5	50	2.2		
			2以上	3,350	27,208	101,367	0	3,768,690	2.04	13,843	7.4	50	3.7		
医療費総額	なし	男性	0	2,096	45,151	103,541	0	2,382,775	−						
			1	4,800	56,351	115,674	0	2,224,531	1.25	11,200	5.4	50	2.7		
			2以上	5,480	73,465	167,183	0	6,529,652	1.63	28,313	15.5	50	7.7		
		女性	0	6,260	31,009	67,144	0	2,049,250	−						
			1	8,732	47,811	134,457	0	5,152,460	1.54	16,803	10.8	50	5.4		
			2以上	6,303	59,124	146,766	0	6,251,620	1.91	28,115	13.1	50	6.6		
	あり	男性	0	283	39,662	69,243	0	544,343	0.88	0					
			1	1,114	56,205	114,373	0	1,799,157	1.24	11,054	1.2	50	0.6	557	0.6
			2以上	2,482	65,445	164,333	0	5,873,738	1.45	20,294	5.0	50	2.5	1241	2.5
		女性	0	758	45,012	291,619	0	7,851,277	1.45	14,003					
			1	2,418	54,028	100,573	0	1,452,821	1.74	23,019	4.1	50	2.1	1209	2.1
			2以上	3,350	60,759	113,691	0	3,814,162	1.96	29,751	7.4	50	3.7	1675	3.7
保健指導での改善が必要な対象者数			肥満者	10,405	人中									4682	人
その肥満者に占める割合														45	%
期待される医療費減少割合(%)			男性												3.1
			女性												5.7

注意：医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が１未満のときは計算せず、０とした。

Ⅲ．研究成果の刊行に関する一覧表・別刷

研究成果の刊行に関する一覧表・別刷

（別刷は総括研究報告、分担研究報告及び P308～312 参照）

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THROMBOSIS RESEARCH

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BRIEF COMMUNICATION

The relation between nicotinamide *N*-methyltransferase gene polymorphism and plasma homocysteine concentration in healthy Japanese men

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Interaction

Dear Sirs,

Hyperhomocysteinemia is established as an independent risk factor for cardiovascular diseases [1,2]. Plasma total homocysteine (tHcy) concentration is influenced by factors such as sex, age, renal function, vitamin intake and inheritance. Several genetic polymorphisms are reported to associate with tHcy concentration, including the most notable methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism.

Recently, a quantitative trait linkage (QTL) analysis on tHcy concentration was conducted in a Spanish family study of venous thrombosis [3]. The chromosome region 11q23 was shown to have a positive linkage signal, and in this region the nicotinamide *N*-methyltransferase (NNMT) gene was located. Subsequent analysis for 10 single nucleotide polymorphisms (SNPs) in the NNMT gene identified one SNP (rs694539 in GenBank, dBSNP database) that was associated with the tHcy concentration. Since the SNP resides in the first intron, the functional significance of it is still unknown. NNMT enzyme activity was shown to have a significant variability among individual, and this difference was attributed not to the structure of the enzyme but to the expression levels of mRNA and protein [4,5]. Thus, this noncoding SNP might be related to the regulation of transcription, which correlates to the phenotype.

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Hence, we wanted to determine whether the reported A/G polymorphism (rs694539) of NNMT gene associates with plasma tHcy concentration in Japanese men. The age, plasma folate, and vitamin B12 concentrations, as well as MTHFR C677T genotype were also examined to detect potential gene–environment, and gene–gene interactions.

Three hundred and thirteen healthy workers of a company in Kanagawa Prefecture in Japan, who underwent a health examination in 2003, were enrolled in the study. None of these subjects had an episode for venous thrombosis, myocardial infarction, stroke or renal failure. The age was 45.8±11.7 years old (mean±S.D.), and body mass index (BMI) was 23.4±3.5 kg/m^2 (mean±S.D.). These values were typical for healthy Japanese male workers. Plasma tHcy, folate and vitamin B12 concentrations were measured using the same methods described by Miyaki et al. [6]. Genotyping was done by polymerase chain reaction (PCR) followed by melting curve analysis using primers 5′-CTGAGGATCTTTATAGTT-GGCT and 5′-ATGACCTGTCCTAAGATCACT, and probes 5′-AATGGATGCAACTAAATGGTTTGGAAAACCCCTCC-Fluorescein and 5′LC Red 640-ACACGAAACTTCTAG-GATTCTAGGAC-Phosphate. The experimental protocol has been described elsewhere [7]. MTHFR C677T polymorphism was determined by PCR followed by *Hinf*I restriction digestion, as previously described [6].

The statistical analyses were carried out using Statistical Package of Social Science for Windows version 11.0 (SPSS Inc., Chicago, IL, USA). The values of $p<0.05$ were considered to indicate statistical significance. Analysis of covariance (ANCOVA) were used to compare the adjusted geometric mean of tHcy according to NNMT genotype under different sub-conditions, and to examine the interactive effects of the gene–environment and gene–gene on tHcy.

The characteristics of the subjects according to NNMT A/G genotypes are shown in Table 1. There were no differences in tHcy, plasma folate and plasma vitamin B12 concentrations between NNMT AA+AG ($n=143$) and GG ($n=170$) genotype groups. However, in the hyperhomocysteinemic subjects (tHcy≥ 13.7 umol/L, as defined by the top 10 percentile) [8] the geometric mean tHcy concentration in the GG group (20.7 umol/L) was significantly higher than the concentration in those with AA+AG group (15.6 umol/L, $p=0.034$) adjusted for age, BMI, plasma folate, vitamin B12 and MTHFR genotype (Table 1).

We examined the effect of plasma folate on tHcy using linear regression models in both NNMT genotypes adjusting for age, BMI, current smoking, drinking, plasma folate, vitamin B12, and MTHFR polymorphism (CC+CT=0, TT=1). We used another model to evaluate the interactive effect in which an interaction term plasma folate×NNMT genotype (AA+AG=0, GG=1) was included and p value for interaction was calculated. Since the age factor is closely associated with elevated tHcy concentrations, where it is relatively stable through the first 4 decades of life, and then tend to rise sharply [9], our analysis was done by stratifying at the age of 40. Only in the elder (age≥40 years) subgroup and not in the younger (age<40) subgroup, the slope of

Table 1 Characteristics of 313 Japanese men according to NNMT genotype

Parameters	Total men	NNMT (AA+AG)	NNMT (GG)	p
% (n)	100 (313)	45.7 (143)	54.3 (170)	
Age (years)	45.8±11.7	45.8±11.3	45.8±12.0	0.957
BMI (kg/m^2)	23.4±3.5	23.4±3.3	23.4±3.7	0.912
Creatinine (mg/dl)	0.9±1.1	0.9±1.2	0.9±1.1	0.547
Plasma variables				
tHcy (umol/L)*	9.7±1.4	9.5±1.3	9.9±1.4	0.219
Multiple adjusted tHcy[1]	9.6±1.0	9.5±1.0	9.8±1.0	0.357
tHcy≥13.7 umol/L[1,2]	18.0±1.1	15.6±1.1	20.7±1.1	0.034
Folate<10.9 nmol/L[1,3]	10.7±1.0	10.3±1.0	11.0±1.0	0.322
VitB12<310.4 pmol/L[1,3]	10.6±1.0	10.9±1.0	10.4±1.0	0.470
Folate (nmol/L)*	13.5±1.5	13.8±1.6	13.3±1.5	0.466
VitB12 (pmol/L)*	364.2±1.4	361.0±1.4	366.9±1.4	0.680
Lifestyle variables				
Current smoking % (n)	59.3 (169)	60.0 (81)	58.7 (88)	0.819
Current drinking % (n)	73.3 (209)	70.4 (95)	76.0 (114)	0.174
MTHFR C677T				
TT% (TT; CC+CT)	14.7 (46; 267)	14.0 (20; 123)	15.3 (26; 144)	0.764

Values are mean±S.D. *Geometric mean±S.D. were calculated on log values and then converted to the ordinary scale. [1] Adjusted for age, BMI, log folate, log Vitamin B12, current smoking, drinking and MTHFR genotype. [2] In the top of 10%. [3] The lowest tertile group.

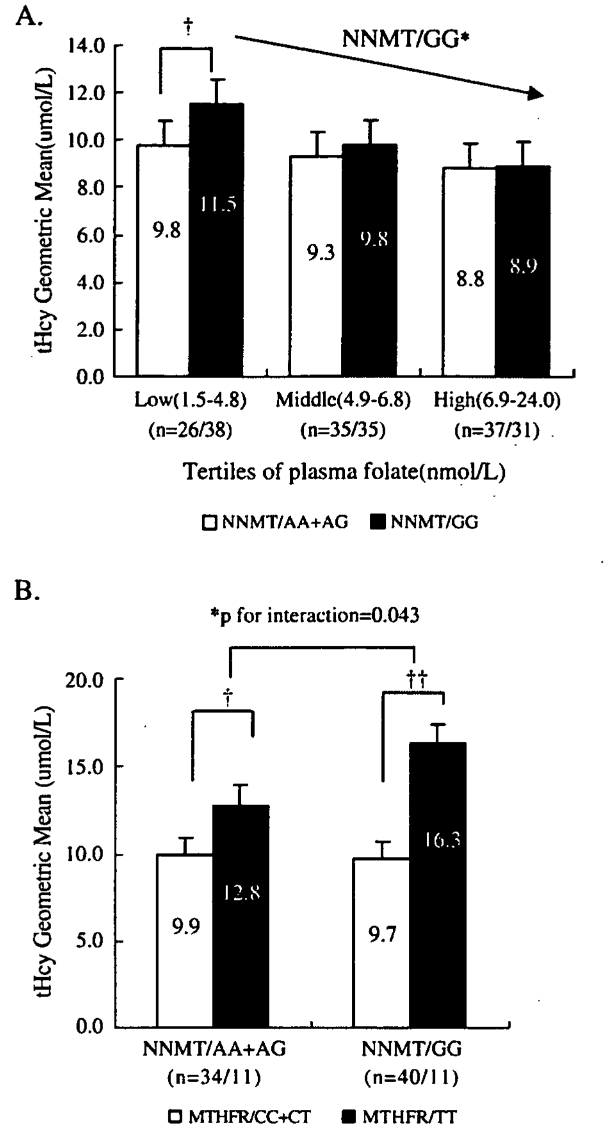

Figure 1 (A) Geometric means of tHcy according to NNMT genotype stratified by tertiles of plasma folate above 40 years healthy Japanese men, adjusted for age, BMI, log folate, log VitB12, current smoking, drinking and MTHFR genotype. † The difference of tHcy between NNMT AA+AG genotype and GG genotype in the lowest tertile plasma folate group (p=0.029). * p for trend test in GG genotype (p=0.028) and in AA+AG genotype (p=0.237). (B) Interaction between MTHFR and NNMT genotypes on tHcy in the lowest tertile plasma folate group (3.4–10.9 nmol/L). Geometric mean of plasma tHcy adjusted for age, BMI, log folate, log Vitamin B12, current smoking and drinking. † The difference of tHcy between MTHFR CC+CT genotype and TT genotype in NNMT AA+AG genotype subjects (p=0.005). †† The difference of tHcy between MTHFR CC+CT genotype and TT genotype in NNMT GG genotype subjects (p<0.001). * The interaction between the NNMT genotype and MTHFR genotype (p=0.043).

the relation between plasma folate and tHcy was significantly differed between the NNMT genotype (GG: β=−0.32, AA+AG: β=−0.08, p for interaction=0.008). We further divided the folate concentration by tertile and got the geometric mean tHcy concentration per tertile (Fig. 1A). At a low plasma folate concentration <10.9 nmol/L (the lowest tertile), GG group had a significantly higher tHcy concentration than AA+AG group (11.5 umol/L vs. 9.8 umol/L, respectively; p=0.029). None of the tHcy concentration differed significantly in the upper two tertile groups. Compared with the AA+AG group, GG group had a steeper significant inverse relationship (p=0.028) between plasma folate and tHcy concentrations.

Furthermore, in the group with plasma folate concentration of <10.9 nmol/L, we found a significant interaction between NNMT A/G and MTHFR C677T genotypes on tHcy (p=0.043) independently of age, BMI, VitB12, smoking and drinking (Fig 1B).

The findings of our study indicate that this polymorphism is not a major determinant of plasma tHcy concentration in healthy Japanese men. Only after taking other confounding factors into account, such as, age, plasma folate concentrations as well as MTHFR C677T polymorphism, did we find a mild relationship between NNMT GG genotype and elevated plasma tHcy concentration.

Our results suggested that 1) NNMT genotype may augment the tHcy concentration in hyperhomocysteinemic subjects (tHcy≥13.7 umol/L), but not in subjects with normal values. 2) In elder subjects (age≥40 years), the NNMT GG genotype had a 1.8 umol/L higher tHcy concentration than AA+AG genotype under low plasma folate level (<10.9 nmol/L), a subgroup that comprised of 22.6% of the total. 3) The difference in plasma tHcy concentration between MTHFR genotypes was modulated by NNMT genotype only in the lowest tertile group (plasma folate < 10.9 nmol/L, p for interaction=0.043), but not in the upper two tertile groups. Some studies show that the MTHFR genotype is correlated with elevated tHcy concentration only when plasma folate concentration is low [10]. It is hypothesized that a higher folate status might enhance the stability of the MTHFR enzyme in vivo, thus reducing the difference in enzyme activity between TT and CC+CT subjects. The result of the present study is consistent with this notion suggesting that the interaction between NNMT and MTHFR genotypes may be dependent on plasma folate concentration.

Our results do not appear to be totally inconsistent with the original report [3]. In their study the effect of the single SNP was not strong, such that it became insignificant after correcting for multiple testing. Their paper also investigated haplotypes consisting of 10 SNPs, and found rare haplotypes including this SNP that have significant association with elevated tHcy concentration, indicating that there might be other causative SNPs. In our study, we did not carry out such intensive SNP haplotyping, since the most provocative haplotype that affects tHcy had an allele frequency of 1.5%, which is too rare to apply for our statistical analysis. More intensive study about the effect of NNMT gene on tHcy concentration is warranted employing detailed haplotyping with a larger population size.

Our study is limited by the particular sampling, which consists of a healthy group of men who are not overweight and had normal values of the blood analytes. Even among the covariates that might be expected to influence plasma tHcy and folate, the relatively high proportion of current smokers and drinkers could contribute to the inability to detect differences.

In conclusion, our results suggest that the NNMT genotype is not a strong determinant of the tHcy concentration but it may have a modifying effect on plasma homocysteine concentration in Japanese men.

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ATHEROSCLEROSIS

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Effect of a 4-year workplace-based physical activity intervention program on the blood lipid profiles of participating employees: The high-risk and population strategy for occupational health promotion (HIPOP-OHP) study

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Abstract

Individuals who are physically fit or engage in regular physical activity have a lower incidence of cardiovascular disease and risk of mortality. We conducted a large-scale controlled trial of interventions to decrease cardiovascular risk factors, during which we assessed the effect of a workplace-based intervention program, which was part of a population strategy for promoting long-term increases in physical activity, on the blood lipid profiles of participating employees. Data were collected from 2929 participants and this report presents the results of a survey conducted in five factories for the intervention group and five factories for the control group at baseline and year 5. The absolute/proportional changes in HDL-cholesterol were 2.7 mg/dL (4.8%) in the intervention group and −0.6 mg/dL (−1.0%) in the control group. The differences between the two groups in the change in serum levels of HDL-cholesterol were highly significant ($p < 0.001$) in each analysis of covariance, in which the number of cigarettes smoked was included or excluded. In the intervention group, the daily walking time increased significantly ($p < 0.001$) when compared between baseline and year 5, whereas no significant difference was observed in daily walking time in the control group over the identical period. Our results show that an intervention program promoting physical activity raises serum HDL-cholesterol levels of middle-aged employees. Increased awareness of the benefits of physical activity, using environmental rearrangement and health promotion campaigns, which especially target walking, may have contributed to a beneficial change in serum HDL-cholesterol levels in the participants.

Keywords: High-density lipoprotein cholesterol; Physical activity; Population strategy; Intervention; Worksite

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1. Introduction

Elevated circulating levels of high-density lipoprotein cholesterol (HDL-C) lower the risk for developing coronary artery disease [1] and are inversely associated with mortality from all causes [2]. Low levels of circulating HDL-C are related significantly and independently to an increased risk of stroke of all types, including ischemic stroke [3].

Regular physical exercise is frequently recommended to prevent coronary artery disease [4]. Improving physical fitness and increasing physical activity are associated with a lower incidence of cardiovascular disease and a reduced risk of mortality [5]. The main mechanism by which regular physical activity mitigates the risk for developing coronary artery disease is its impact on HDL metabolism [6]. Several authors have explored the effect of exercise on changes in HDL-C levels [7], and the collective results of these studies have shown that modifications in lifestyle are thought to be beneficial in increasing serum HDL-C levels [2,8].

Given that most of the adult population is employed, the workplace presents an ideal opportunity to reach large numbers of people for the purpose of promoting good health and preventing disease [9]. However, there are only a few published reports of controlled trials that were conducted in the workplace and whose aim was to increase the physical activity of the employees. Shimizu et al. [10] investigated the relationship between an interview-based health promotion program and the risk for developing cardiovascular disease in the workplace. From their findings, they suggested that changes in health-related behavior of the participants, including increases in physical activity, were the basis for increased levels of HDL-C in middle-aged participants. However, it remains unclear how a population strategy that promotes good health by increasing physical activity can influence participants in the workplace [11].

In the current study, we assessed the effect of a workplace-based intervention program on the blood lipid profiles of participating employees as part of a population strategy for promoting long-term increases in physical activity.

2. Participants and methods

2.1. Study population

A large intervention trial, the high-risk and population strategy for occupational health promotion (HIPOP-OHP) study, was conducted; its details have been published elsewhere [12,13]. For this purpose, companies throughout Japan were recruited to participate in the study. The first allocation was modified with the hope that each company would comply with the aims and conditions of the study. Twelve participating companies, which consisted of two non-factory companies and 10 factories, were either assigned to an intervention group or a control group. In those companies that were assigned to the intervention group, the health-related environment was improved using a population strategy and individual interventions (high-risk strategy). In those companies that were assigned to the control group, the company was provided only with individual intervention teaching material. Each group consisted of one non-factory company and five factories. The baseline survey was conducted between 1999 and 2000, and the intervention program was done between 2000 and 2004.

The non-factory company in the intervention group was not followed up in year 5 of the study because of a corporate merger. Therefore, we excluded the non-factory company from each group for the purposes of analysis. As a result, baseline and year 5 HDL-C data from the 10 remaining companies were analyzed. Although about 32% of the participants were moved from their worksites during the 4 years, the return participation rates were similar between the intervention and the control group (68 and 69%). In the intervention group of five companies, there were 807 male and 270 female participants, and in the control group of five companies, there were 1588 male and 264 female participants. The population strategy for health promotion focused on three areas: nutrition, physical activity, and cigarette smoking. For health promoting target, a research team was organized to support the strategy.

For physical activity, three types of intervention were planned: (a) a presentation of information on physical activity, (b) a campaign to increase physical activity, and (c) providing tools for walking (Table 1). Specifically, weekly freestanding mini-poster presentations were set up in the cafeteria of the participating companies. An 'active point campaign' using pedometers was carried out twice a year, continued for 2 months on each occasion, in order to increase the individual physical activity of each employee. The frequency and duration of the 'active point campaign' were modified slightly according to the employment-related con-

Table 1
Intervention methods for physical activity at five companies in the intervention group, HIPOP-OHP Study, Japan, for 1999–2004 (N = 2929)

Presenting information on physical activity	Campaign to increase physical activity	Providing tools for walking
• Weekly freestanding mini-poster presentation at point-of-purchase or adjacent to the advertising menu	• Self-recorded diary of physical activity and 'active point campaign'	• Constructed path for walking at the workplace
• Wall poster	• Lecture and instruction on 'active walking'	• Distribution of maps for walking at the workplace
• Web-site	• Lecture and instruction on 'stretching'	• Pedometers
• Intra-workplace newspaper	• Lecture and instruction on 'dumbbell exercises'	
	• Sporting events at the workplace	

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ditions at each company. The participation rates of the employees at each company in the 'active point campaign' were set to be at least 50%. Outdoor or indoor walking paths were constructed on company property. If it was difficult to construct these paths, information on suitable walking courses near the company property and/or maps showing suitable walks were provided. As part of the high-risk strategy, individual 6-month health education instruction was provided for those participants who had either high-normal or elevated levels of blood pressure, hypercholesterolemia, or elevated plasma glucose levels.

Informed consent was obtained from the participants regarding individual guidance for the high-risk strategy. This study was performed as part of the management of safety and health in each company. 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).

2.2. Data collection

Biologic data were collected during annual health examinations, and included blood pressure measurements and serum total lipid and HDL-C levels. To measure the lipid levels in each participant, the company established a contract with a clinical laboratory; the blood testing was standardized through the US Cholesterol Reference Method Laboratory Network (CRMLN) [14]. Duplicate measurements of blood pressure were obtained from each participant, after he or she had rested quietly for exactly 5 min, using a calibrated automatic sphygmomanometer (BP-103iII; Nippon Colin, Komaki, Japan). The average value of the two measurements was used in the analysis.

Each participant was given a questionnaire in which they were asked to provide information regarding their daily physical activity, awareness of increasing their physical activity, such as their daily walking, and other lifestyle parameters, such as daily alcohol intake and their smoking habits. The information on daily walking times was obtained by each participant completing a questionnaire. Alcohol consumption was quantified and expressed in grams per day.

2.3. Data analysis

All statistical analyses, including analysis of covariance (ANCOVA), were performed using SPSS for Windows, version 12.0 (Statistical Product and Service Solutions, Chicago, IL, USA), and statistical significance was set at 5%. The ANCOVA (Model 1) was first adjusted for changes in the level of each risk factor, including alcohol consumption, the number of cigarettes smoked per day, body mass index (BMI), age, gender, medical treatment for hypercholesterolemia, and HDL-C, between baseline and year 5 for each participant. A second model omitted the change in the number of cigarettes smoked per day (Model 2).

The differences in the distributions of the two groups at baseline and at year 5 were analyzed using the χ^2-test for proportions for four levels of daily walking times.

3. Results

The average age at baseline was 42.7 ± 8.9 (males, 42.2 ± 9.1; females, 44.2 ± 8.0) and 39.8 ± 8.7 (males, 39.9 ± 8.9; females, 39.5 ± 7.6) years for the intervention and control groups, respectively. The clinical characteristics of the participants in the two groups at baseline and at year 5 are summarized in Table 2. At baseline, there were significant differences in age, serum HDL-C levels, and serum non-HDL-C levels between the two groups of participants. For female participants, the BMI was significantly higher in the intervention group than in the control group at baseline. The proportions of current alcohol consumers and cigarette smokers in the intervention group were higher than in the control group for males, but the proportions for females in the intervention group lower than in the control group. The proportion of the overall study population that was treated for hypercholesterolemia during the trial was 6.1% (51 males and 15 females) in the intervention group and 4.5% (74 males and nine females) in the control group.

Increased plasma HDL-C levels were measured in the intervention group between the baseline and year 5. The non-HDL-C levels increased and the number of cigarettes smoked per day decreased in both groups when baseline values were compared with those in year 5. However, the mean BMI did not change in either group between the baseline and year 5. The proportion of current alcohol consumers decreased in the control group.

As shown in Table 3, the differences in the changes in serum HDL-C levels for the two groups were highly significant ($p < 0.001$) in each model when adjusted for potential confounding variables, with or without inclusion of the change in the number of cigarettes smoked; the intervention resulted in an increase in HDL-C levels. The study site did not affect this result. HDL-C increase was observed in all sites in the intervention group except one. After excluding this site, significant differences in the changes in serum HDL-C levels for the two groups were also detected in the ANCOVA (range of the differences, 2.4–5.1 mg/dL).

The proportion of the overall population that was aware of increasing their daily walking time was 31.3 and 24.2% in the intervention and control groups, respectively, at year 5. A significant difference existed between the two groups ($p < 0.001$). Table 4 shows the distribution of walking time per day measured by the two self-reported questionnaires. At the inception of the study, both groups contained similar proportions of individuals whose daily walking times were less than 30 min (intervention group, 13.5%; control group, 14.6%). A significant difference ($p < 0.001$) in this study parameter existed between the two groups at year 5. The percentage of participants who increased their daily walking

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Table 2
Means or medians and prevalences[a] of the participants' characteristics in 10 companies at baseline and year 5, HIPOP-OHP Study, Japan, for 1999–2004 ($N=2929$)

Characteristics		Intervention ($N=1077$)		Control ($N=1852$)	
		Baseline	Year 5	Baseline	Year 5
HDL-C (mg/dL)	Male	54.8 (14.7)	56.9 (16.3)	56.1 (13.0)	56.3 (13.6)
	Female	63.5 (14.1)	68.1 (16.2)	66.7 (13.1)	64.1 (12.6)
Non-HDL-C (mg/dL)	Male	145.1 (36.2)	148.6 (35.8)	138.1 (35.5)	141.8 (35.6)
	Female	135.5 (33.4)	143.3 (35.7)	119.0 (31.1)	127.2 (32.8)
Systolic blood pressure (mmHg)	Male	120.0 (18.7)	122.8 (19.5)	121.6 (17.0)	121.8 (18.3)
	Female	115.8 (19.1)	117.0 (20.0)	114.1 (16.3)	114.1 (18.6)
Diastolic blood pressure (mmHg)	Male	74.1 (12.3)	76.4 (13.4)	74.2 (13.4)	74.6 (12.1)
	Female	69.8 (12.5)	70.3 (11.9)	67.4 (10.5)	69.7 (12.4)
Body mass index (BMI, kg/m)	Male	23.2 (3.2)	23.5 (3.4)	23.1 (2.9)	23.2 (2.9)
	Female	22.7 (4.0)	22.7 (4.1)	22.0 (3.6)	22.1 (3.7)
Consumer of alcohol (%)	Male	65.6	66.1	63.9	61.4
	Female	20.9	22.3	27.5	22.6
Alcohol consumption (g/day[b])	Male	10.8 (0.0–36.6)	9.0 (0.0–36.0)	9.9 (0.0–31.6)	8.0 (0.0–32.0)
	Female	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.0 (0.0–0.0)
Cigarette smoker (%)	Male	57.8	48.9	56.8	51.6
	Female	7.2	7.4	11.1	8.8
Number of cigarettes per day	Male	12.6 (12.6)	10.2 (12.2)	11.4 (11.4)	9.6 (10.9)
	Female	0.9 (3.7)	0.8 (3.2)	1.3 (4.0)	0.9 (3.3)

[a] The numbers in parentheses are interquartile ranges for alcohol consumption and standard deviation for other variables.
[b] Median.

Table 3
Changes in HDL-C between baseline and at year 5 in the two groups, HIPOP-OHP Study, Japan, for 1999–2004 ($N=2929$)

Group	Model 1[a]				Model 2[b]			
	Mean[c]	S.E.	Difference (95% CI)	p	Mean[d]	S.E.	Difference (95% CI)	p
Intervention (five companies)	2.71	0.29	3.29	<0.001	2.85	0.28	3.42	<0.001
Control (five companies)	−0.58	0.21	(2.59–3.99)		−0.57	0.21	(2.73–4.11)	

[a] Adjusted increase in HDL-C (mg/dL) between baseline and at year 5.
[b] Adjusted increase in HDL-C (mg/dL) between baseline and at year 5 (excluding the change in the number of cigarettes).
[c] Adjusted for age at baseline, gender, changes in the number of cigarettes smoked per day, changes in the consumption of alcohol per day, changes in BMI, treatment for hypercholesterolemia, and HDL-C at baseline.
[d] Adjusted for age at baseline, gender, changes in the consumption of alcohol per day, BMI, treatment for hypercholesterolemia, and HDL-C at baseline.

Table 4
Proportion of time spent walking per day at baseline and at year 5 in the two groups, HIPOP-OHP Study, Japan, for 1999–2004 ($N=2929$)

Group		Walking time per day (min)				Total %	p
		<30	30–59	60–119	≧120		
Intervention (five companies)	Baseline (%)	13.5	25.8	23.8	36.9	100	<0.001
	Year 5 (%)	8.2	24.8	26.8	40.2	100	
Control (five companies)	Baseline (%)	14.6	31.4	24.5	29.5	100	n.s.
	Year 5 (%)	15.1	31.6	24.2	29.1	100	

time was 28.9% in the intervention group and 25.5% in the control group, whereas the percentage of participants who decreased their walking time was 18.6% (intervention group) and 25.7% (control group). In the intervention group, the daily walking times increased significantly from baseline to year 5, whereas no significant difference was found between the daily walking times at baseline and at year 5 in the control group.

4. Discussion

We explored the effect of a 4-year intervention program on the employees in five factories in an effort to promote physical activity, irrespective of the employee's serum lipid status. We observed that increasing physical activity raised serum HDL-C levels. Our intervention for physical activity was not of high intensity and was conducted as part of a population

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strategy in an attempt to induce individuals to change their behavior by increasing their interest and motivation. Therefore, the results of this study can serve as a reference when considering the implementation of workplace programs to decrease cardiovascular risk factors.

Choudhury et al. [15] found that cigarette smoking was associated with lower serum HDL-C levels than those found in non-smoking individuals. In a follow-up study, Martinez-Gonzalez et al. [16] reported that leisure-time exercise and smoking cessation were each associated with increased serum HDL-C levels. In addition to physical activity, other physiological and lifestyle characteristics, such as the degree of obesity, cigarette smoking, and alcohol consumption, influence the plasma levels of HDL-C [17]. Ellison et al. [18] found significant differences in serum HDL-C levels according to the total number of minutes per day of leisure-time physical activity, after adjusting for alcohol consumption and cigarette smoking. Increased physical activity and the cessation of smoking confer many benefits beyond their effects on HDL-C [18].

Cessation of cigarette smoking can potentially increase serum HDL-C levels. The population strategy for smoking cessation was successful in this intervention program, as reported previously [19]. The changes in serum HDL-C levels in the analyses that did or did not take into account cigarette smoking were 2.71 and 2.85 mg/dL, respectively, for the intervention group and −0.58 and −0.57 mg/dL, respectively, for the control group. The analyses both showed statistically significant differences between two groups. Therefore, smoking cessation was not likely to be the sole cause for the decline in serum HDL-C levels. It was not discrepant with the fact which the effect of the anti-smoking campaign was only limited to smokers.

Only a few studies have reported the use of diet modification to increase serum HDL-C levels. The results of one meta-analysis reported that increasing the daily intake of lauric acid, which is a major component of the oils in tropical fruits and is found in coconut and palm kernel fat, raises serum HDL-C levels [20]. Furthermore, Okuda et al. [21] reported that dietary intake of n-3 polyunsaturated fatty acids (n3 PUFA) was positively associated with the serum level of HDL-C in males. Moreover, they also reported that a strong association between serum HDL-C levels and dietary intake of tropical oils or n-3 PUFA does not exist, and that the use of tropical oils in Japan is very rare. Although the current study targeted nutritional intervention, the advice to reduce salt intake and increase potassium intake was intended mainly to reduce blood pressure [22,23]. Therefore, daily nutritional intake may not have played a major role in the changes in serum HDL-C levels.

The change in serum HDL-C levels found in this study is assumed to reflect a heightened awareness of the benefits of exercise. Exercise programs of a longer duration and greater exercise volume have increased HDL-C levels [24], and this increase has been reported in studies conducted over a longer period [25]. Increased awareness of physical activity, including walking, may also have fueled the changes observed among the participants in the intervention group. It is now thought that low-intensity physical activity, such as walking, may achieve some of the same benefits as more vigorous activity and be more acceptable to most people [26].

Previous reports on the results from randomized trials dealing with the effects of walking on serum lipid levels in adults have described conflicting results [27,28]. Barengo et al. [29] reported that not only leisure-time physical activity but also commuting activity was directly associated with serum HDL-C levels. It has been suggested that all forms of physical activity should be promoted to reduce the number of individuals with cardiovascular diseases in the population [29]. In this trial, increasing all forms of physical activity, not only walking, may have increased the serum HDL-C level. However, increasing the daily walking time to more than 30 min most likely played an important role in the improvement. This result demonstrates the effectiveness of the study, which included interventions to increase physical activity, such as walking time and during commuting.

One of the limitations of this study was that individual-level randomization was not possible. Random allocation of the companies was initially attempted. However, some companies were forced to withdraw from the study because of either bankruptcy or opposition from board members to their participation. Eventually, we modified the first allocation based on the hope that each company would be able to comply with the aims and conditions of the study. Second, any changes in physical activity were self-assessed using a questionnaire and they could not be defined quantitatively.

This study did not provide accurate information on individual changes in physical activity, although the results suggest that a change in awareness and behavior in the intervention group had occurred. The absence of any changes in alcohol consumption or BMI during the trial, and the predicted small effect of the daily nutritional intake on increases in serum HDL-C levels, suggest that promoting physical activity led to the increase in serum HDL-C levels. Further study is needed to focus on the individual assessment of physical activity in order to confirm our findings.

In summary, our results show that interventions promoting physical activity help to raise the serum HDL-C levels of middle-aged employees. Increased awareness of physical activities, environmental rearrangement, and the introduction of campaigns, especially those that target walking, may contribute to beneficial changes in serum HDL-C levels.

Acknowledgments

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Appendix A

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065

RELATION BETWEEN BODY MASS INDEX AND TOTAL MORTALITY IN JAPAN. POOLING PROJECT OF 190,000 JAPANESE PARTICIPANTS FROM COHORT STUDIES (EPOCH-JAPAN). *Y Murakami, T Okamura, H Ueshima and Evidences for cardiovascular Prevention from Observational CoHorts in JAPAN (EPOCH-JAPAN) Study Research Group (Department of Health Science, Shiga University of Medical Science, Japan)

WHO advocated that Asian population might have lower BMI cut off level as normal weight than Westerners. However, it is still unknown whether Japanese BMI cut off for normal BMI should be lower than 25. Thirteen prospective cohort study in which participants laboratory data were collected at the baseline survey were enrolled and total 188,321 participants (men: 70,613 women: 117,708, mean follow up periods: 9.8 years) who aged from 40 to 90 were included in the analysis. We divided the participants into ten groups according to BMI and the reference group was set in the lowest. Poisson regression model was used to estimate multivariate adjusted hazard ratio (HR) according to BMI categories. Smoking, drinking, systolic blood pressure and the cohort were adjusted in the model. After checking the pattern of gender-specific hazard ratios, common results were estimated from the model above. High hazard ratios were observed both underweight group (BMI < 18.5: HR (men:1.81, women: 1.61)) and obesity group (BMI ≥ 30: HR: (men:1.12, women: 1.33)). The sex adjusted HR showed the significant results (BMI < 18.5: 1.69, BMI ≥ 30: 1.24) and relation between BMI categories and hazard ratio were U-shaped. The lowest HR was observed in BMI category 24.0–24.9 in men and 23.0–23.9 in women. These results remain same (BMI < 18.5: HR $= 1.82$, BMI ≥ 30.0: HR $=$ 1.29) when we exclude the five years observation period from data. We examined U-shaped relation between BMI and total mortality and these remained same even we excluded potentially frail participants.

066-S

SMOKING PREVALENCE AND PERCEIVED EFFECTIVENESS OF SMOKING POLICY AND COUNSELING PATIENTS ABOUT SMOKING AMONG MEDICAL STUDENTS IN AMMAN, JORDAN. R Merrill, H Madanat, *E Cox, J Merrill (Brigham Young University, Provo, UT, 84606)

This study identifies prevalence of smoking among 340 first and fourth year medical students in Amman, Jordan, and their perceived effectiveness of physicians counseling patients about smoking according to smoking status and year in medical school. Smoking prevalence among medical students in Jordan (26% for males and 7% for females) is similar to that of their peers in the general population. Students who smoke or who are male are less likely to believe it is wrong for physicians to smoke in front of patients or that smoking policy or physician interaction with patients can influence smoking prevention and control. Students believe that physicians can more effectively prevent smoking than influencing patients to stop smoking. Training on how to effectively counsel patients about smoking prevention and cessation is warranted in this population of future physicians.

067-S

SMOKING PREVALENCE, ATTITUDES, AND PERCEIVED SMOKING PREVENTION AND CONTROL RESPONSIBILITIES AND BEHAVIORS AMONG PHYSICIANS IN JORDAN. R Merrill, H Madanat, *J Layton, C Madsen, C Hanson (Brigham Young University, Provo, UT 84602)

Purpose: Physicians can play an effective role in smoking prevention and control. This study identifies smoking prevalence among physicians in Jordan. It also assesses their attitudes and smoking prevention and control responsibilities and behaviors. Methods: A cross-sectional survey was administered among 251 physicians from public and private hospitals in Jordan. There was 67% response rate. Results: The prevalence of smoking is 22.4% for male physicians and 9.1% for female physicians. Among current or former smokers, 81.1% (n = 73), 29.1% overall, had smoked in front of a patient. The physicians believed that physician counseling could more effectively prevent patients from smoking than influencing patients to quit smoking. Approximately 56.2% of physicians had ever counseled patients about smoking and 34.3% regularly counseled patients about smoking. Only 18.3% (n = 46) had received training, either in medical school or thereafter, on counseling patients about smoking. Physicians with training on counseling patients about smoking cessation were significantly more likely to have counseled or to routinely counsel patients to help them quit or not start smoking. Training also lowered the percentage of smokers who smoked in front of patients. Conclusion: Training programs for physicians on patient counseling about smoking are efficacious, and a higher percentage of physicians should be exposed to these programs.

068-S

SMOKING PREVALENCE, ATTITUDES, AND PERCEIVED SMOKING PREVENTION AND CONTROL RESPONSIBILITIES AND PRACTICES AMONG NURSES IN AMMAN, JORDAN. R Merrill, H Madanat, *A T Kelley (Brigham Young University, Provo, UT 84602)

This study assesses smoking prevalence, attitudes, and perceived patient counseling responsibilities among practicing nurses in Amman, Jordan. It also identifies whether the smoking status or their training with respect to counseling patients about smoking is associated with their smoking-related attitudes and counseling practices. Data were collected through a cross-sectional survey of 266 (57% males and 43% females) nurses at four public and private hospitals in Amman. Smoking prevalence was 42% for male nurses and 13% for female nurses. Nurses strongly favored enforcement of anti-smoking policy, but did not strongly agree that nurses should be involved in counseling patients about smoking. Approximately 41% of nurses indicated that they had received training on counseling patients about smoking. Nurse training with respect to counseling patients about smoking was positively associated with the nurses' belief that their counseling could help patients stop or never start smoking. In addition, nurses with counseling training about smoking felt significantly better prepared to assist patients to quit smoking. Nurses who smoked were significantly less likely to believe their counseling of patients about smoking could be effective. Finally, smoking status was not significantly associated with how prepared nurses felt they were to assist patients to quit smoking. These findings identify a need for more extensive and better-tailored training programs for nurses on patient counseling about smoking.

* = Presenter; S = The work was completed while the presenter was a student