The Mierlo Project : risk factors for cardiovascular diseases in a primary care population: their interrelationships, clinical outcomes and responses to intervention

THE MIERLO PROJECT

RISK FACTORS FOR CARDIOVASCULAR DISEASES IN A PRIMARY CARE POPULATION: THEIR INTERRELATIONSHIPS, CLINICAL OUTCOMES AND RESPONSES TO INTERVENTION

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RISK FACTORS FOR CARDIOVASCULAR DISEASES IN A PRIMARY CARE POPULATION: THEIR INTERRELATIONSHIPS, CLINICAL OUTCOMES AND RESPONSES TO INTERVENTION

PROEFSCHRIFT

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CONTENT

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CHAPTER 1

INTRODUCTION

1.1 Risk factors for cardiovascular disease

Of all diseases, cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, has the highest morbidity and mortality in Western countries. In the last decades, great efforts have been made to reduce this high prevalence. As such, prevention of CVD is considered an important task for physicians, especially in primary care.[1]

Identifying risk factors is an important prerequisite to primary prevention. The Framingham Heart Study, started in 1948, has contributed greatly to our understanding of the significance of risk factors for CVD.[2] Among approximately 200 risk factors[3], generally recognized risk factors for CHD currently include older age, male gender, positive family history, smoking habits, hypertension (in particular systolic hypertension[4]), hypercholesterolemia and diabetes mellitus (DM). Related lipemic parameters which are recognized as risk factors for CHD are elevated levels of low density lipoprotein cholesterol (LDL-C)[1,3], triglycerides (TG)[1,3,5], apolipoprotein-B (Apo-B)[1,6] and lipoprotein(a) Lp(a)[1,3] and decreased levels of high density lipoprotein cholesterol (HDL-C)[1,3] and apolipoprotein-A1 (Apo-A1)[6]. Additionally, elevated fibrinogen (FB) levels are nowadays considered to be an independent risk factor.[1,7,8]

In the case of stroke, the factor most generally recognized as the principal risk factor is hypertension.[9] Other risk factors include myocardial infarction (MI), especially in the first month after the event, DM and smoking. Dyslipidemia, including hypercholesterolemia, has not been clearly established as a risk factor, although some studies with the lipid-lowering 3-hydroxy-3-methylglutaryl coenzyme A reductase agents (statins) have shown a decrease in the risk of stroke after MI.[10,11] Recently the EUROSTROKE Project has identified high FB level as a powerful predictor of stroke.[12]

Psychosocial factors in relation to CVD risk have been investigated to a much lesser extent than the above-mentioned 'standard' risk factors. It has been observed that many patients feel tired, distressed or even depressed after an MI.[13,14] Epidemiological studies investigating the prodomata of MI have shown that these feelings already existed before the MI in the majority of patients.[15] This prodromal state was labeled by *Appels* as 'vital exhaustion', a state characterized by unusual fatigue, loss of energy, increased irritability and feelings of demoralization.[16]

Fatigue, defined as a feeling of physical tiredness and lack of energy,

is also a common problem after stroke.[17] It is an unresolved question whether such fatigue is a consequence or one of the preconditions of stroke.

1.2 Situation in Dutch general practice

In the Netherlands, recommendations for the treatment and diagnosis of diseases prevalent in general practice have been developed by the Dutch College of General Practitioners (NHG). The purpose of these 'NHG Practice Guidelines' is to increase the quality of primary medical care. With regard to CVD risk factors, two standards have been developed: an NHG Practice Guideline on Cholesterol[18] and an NHG Practice Guideline on Hypertension.[19] These two guidelines provide recommendations for the identification and modification of the risk factors, while prevention is outside the scope of these Guidelines. General screening as such is not considered useful for primary prevention purposes. Instead, subjects at risk are identified as part of the daily general practice routine, in close relation with other cardiovascular diseases, diabetes mellitus, obesity and other CVD risk factors, especially smoking. However, the NHG Practice Guideline on Hypertension does recommend check-ups every five years by the general practitioner (GP) for subjects older than 60 years and annual check-ups for subjects with borderline hypertension.

According to the NHG Practice Guideline on Cholesterol, identification of hypercholesterolemic subjects should only be done among people with a known high risk of CVD (like those suffering from DM, with known family history). Psychosocial factors are not mentioned in either of the NHG guidelines, so the NHG makes no recommendations in this respect for GPs.

1.3 Estimation of cardiovascular risk

It is generally recognized, as the NHG Practice Guidelines also state, that CVD is multifactorial in origin.[1] Nowadays, the emphasis is on considering the absolute risk, rather than the relative risk of individual risk factors. Methods have been developed to estimate the risk in an

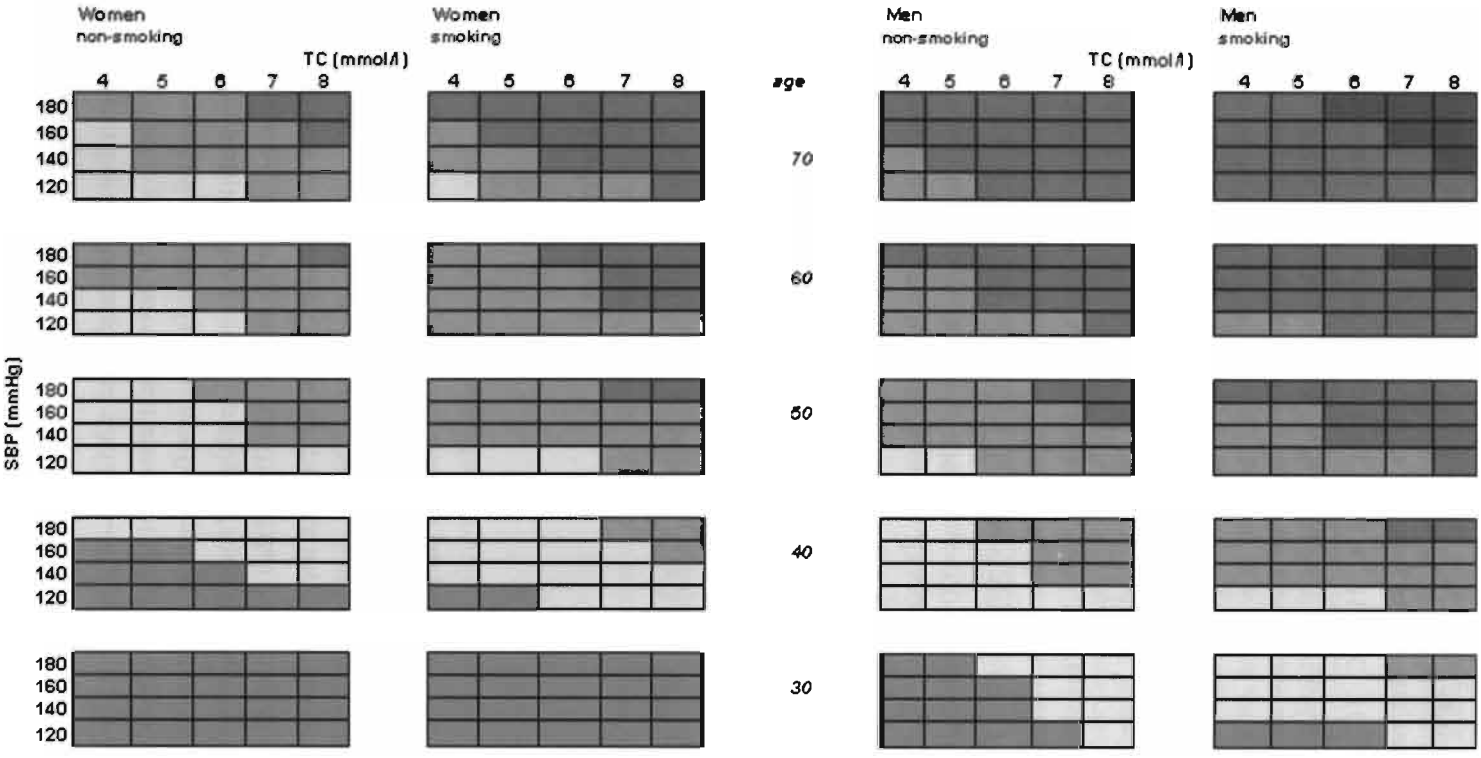
apparently healthy individual, mainly based on or derived from the data of the Framingham study.[2] *The British Medical Journal* has published a special issue *(no. 7236; 11 March, 2000)* featuring papers and debates on these biometric models and their applications in general practice. Additionally, a 2003 study compared four different models, including the current UK guidelines, for identifying individuals at increased risk of CHD from the general population, without a history of MI, stroke or angina.[20] The study used the Framingham 10-year CHD risk equation (>15% risk to get CHD within 10 years)[2] as a 'gold standard'. Its population was comparable to that in the Mierlo Project described in the present thesis: 6307 men and women aged between 30 and 74 years.

Of these biometric models, the Coronary Risk Chart (CRC) has been developed by Task Forces of the *European Society of Cardiology*, the *European Atherosclerosis Society and the European Society of Hypertension* on prevention of CHD in clinical practice.[1] This chart allows a simple CHD risk estimate to be made for an individual in general practice. The CRC is subdivided into 20 blocks, based on the variables gender (M/F), age (30-80 y) and smoker/non-smoker (S/NS). The blocks are subdivided into smaller parts on the basis of the systolic blood pressure (SBP) and total cholesterol (TC) (see figure 1.1). The CRC estimates a healthy person's absolute 10-year risk of a CHD event (angina pectoris, non-fatal MI, or coronary death). Healthy high-risk individuals are defined as those whose 10-year CHD risk exceeds 20% (the same definition as that used in the NHG Practice Guideline on Hypertension, third revision[19]), or will exceed 20% if projected to the age of 60 years, and is sustained despite professional lifestyle intervention. The CRC cannot be applied to subjects who have already developed symptomatic CHD or other atherosclerotic disease, nor to diabetic patients, since their CHD risk is more than double that of non-diabetic subjects.

1.4 Identification of individuals at risk

Before the GP can advise an individual to reduce his or her CVD risk, it is obvious that this individual has to be identified as being at risk. In primary care, finding individuals at high CVD risk remains a challenge. Neither of the NHG Practice Guidelines recommends general screening.[18,19]

Figure 1.1 Coronary Risk Chart for Primary Prevention (CRC)



TC: total cholesterol; SBP: systolic blood pressure
TC from mmol/l to mg/dl: multiply by 38.67

The European Task Force states that since full-scale action is not possible within a short period of time[1], the highest priority should be given to patients with clinically established CVD.

Since 1992, efforts have been made in the Netherlands to develop a workable model to identify apparently healthy subjects at risk in a primary care setting. The project, entitled 'Preventie: maatwerk'[21] (tailored prevention) is an initiative of the NHG and the National Association of General Practitioners (LHV). Another project, entitled 'Hartslag Limburg'[22] (Limburg heartbeat, named after the Dutch province of Limburg where it is being implemented) is a project within the framework of WHO's 'Towards Unity for Health' project. GPs are playing major roles in both projects.[21,22]

1.5 The Mierlo Project

Since CVD is multifactorial in nature, The Mierlo Project studied risk factors for CVD in a primary care population, together with their interrelationships, clinical outcomes and responses to intervention. For this purpose, we started a selection procedure among approximately 6000 adults in an average Dutch village, Mierlo, in 1993. Mierlo was chosen since all local GPs, who were running a joint practice in one health center, were willing to participate in this project. The selection procedure was performed between 1993 and 1995, and was followed by a one-year intervention study with a lipid-lowering agent. This intervention lasted till 1996. End points of MI and stroke were assessed in 1998.

The objectives of the Mierlo Project were to determine:

1. the influence of smoking on lipid values and FB;
2. whether vital exhaustion is a risk factor for MI and stroke; and
3. whether magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) reduces TC, other lipid values and FB.

The first part of the project consisted of two cross-sectional studies among hypercholesterolemic subjects, examining the interrelationships between smoking on the one hand and LDL-C, HDL-C, TG and FB on the other in this cohort. Special attention was paid to the relation with gender and age. These two studies are described in **chapters 4 and 5**.

The second part of the Mierlo Project examined the predictive value

of a state of vital exhaustion, among other CVD risk factors, for MI and first stroke. These prospective studies are discussed in **chapters 6 and 7**.

The third part of the project concerned a randomized placebo-controlled, double-blind study with the lipid-lowering agent MPPG, a vitamin B6 derivative. It examined the effect of this compound on TC, LDL-C, HDL-C, TG, Apo-A1, Apo-B, lp(a) and FB, as well as its side effects. In addition to the effects of MPPG, its acceptance by hypercholesterolemic individuals in a primary care setting was also addressed (effectiveness). This clinical trial is described in **chapter 8**.

A general discussion about what we have learned from the Mierlo Project and what it may mean for the prevention of CVD in primary care and for future research is given in **chapter 9** of this thesis.

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CHAPTER 2

DESIGN OF THE MIERLO PROJECT

2.1. Setting

The Mierlo Project was conducted between 1993 and 1998 in Mierlo, a village with approximately 10,000 inhabitants, 15 km south-east of the town of Eindhoven (in the southern part of the Netherlands). Prior to the randomized placebo-controlled double-blind intervention trial (RCT), the entire adult population of this village entered a selection protocol aimed at detecting subjects at increased risk of cardiovascular disease (CVD). Enrollment in the RCT took place simultaneously with the selection part of the study. Figure 2.1 shows the time schedule of the project.

In Mierlo, five general practitioners (GPs) collaborate in one health center, which also houses the local pharmacy. The selection procedure was conducted at one location in the village, separated from the health center and specially equipped for this purpose. At this selection center, one experienced practice-research nurse and one previously trained research nurse were responsible for the logistics (mailings, making appointments, transporting blood samples) and the assessment of blood pressure and the anthropometric parameters of height and weight. They implemented the blood sampling procedure and also asked the subjects about their physical activities and smoking habits. Their training was based on the relevant Practice Guidelines of the Dutch College of General Practitioners (NHG).[1,2]

The selection period started with the mailing of a simple questionnaire regarding factors related to CVD to the population of Mierlo aged 26 to 66 (t_{-4}) (figure 2.1). On the basis of the outcome of this questionnaire, individuals were invited for a first visit (t_{-3}). The subpopulation aged between 41 and 66 years were administered the Maastricht Interview on Vital Exhaustion (MIVE; appendix) to establish the extent of any vital exhaustion.[3] Two prospective cohort studies were carried out, one to investigate whether vital exhaustion is a precursor of first stroke and the other to investigate whether vital exhaustion assessment contributes to the identification of subjects at increased risk of myocardial infarction (MI).

In the hypercholesterolemic cohort, two studies were performed at the third visit (t_{-1}), one to investigate the effect of smoking on HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and triglycerides (TG),

Figure 2.1. Overall organization of the Mierlo Project.

	selection at selection center				intervention and follow-up by GPs						endpoint
t (month)	(-4)*	(-3)*	(-2)*	(-1)*	0	1	3	6	9	12	50.8 (median)
Registered in database	x										
Questionnaire	x										
Blood pressure – systolic (2x)		x	x	x		x	x	x	x	x	
Blood pressure – diastolic (2x)		x	x	x		x	x	x	x	x	
Weight		x	x	x		x	x	x	x	x	
Height		x									
Body Mass Index		x	x	x							
Smoking habits		x	x	x		x	x	x	x	x	
Exercise habits		x	x	x		x	x	x	x	x	
Informed consent					x						
In/exclusion					x						
Total-cholesterol		x	x	x		x	x	x	x	x	
HDL-cholesterol				x		x	x	x	x	x	
LDL-cholesterol (Friedewald)				x		x	x	x	x	x	
Triglycerides				x		x	x	x	x	x	
Fibrinogen				x		x	x	x	x	x	
GP Consultation					x	x	x	x	x	x	
Written consultation					x						
MPPG/placebo handed out					x		x	x	x		
MPPG/placebo intake							x	x	x	x	
Pill count							x	x	x	x	
Termination form						any moment					
Assessment of Vital Exhaustion		x$									
Assessment of first stroke											x$
Assessment of myocardial infarction											x$

* *not necessarily one month*
$ *subjects between 41 and 66 years (at t_{-3})*

and the other to investigate the effect of smoking on fibrinogen (FB) levels.

The RCT with magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) was conducted by the five GPs (while blood sampling remained the task of the two nurses at the selection center). Each GP was responsible for those patients registered with him or her. One GP was also responsible

for a group of patients who were registered with a GP outside the village, or who were not registered with any GP at all. The pharmacy's task was the storage and supply of the trial medication.

All blood samples were analyzed at the laboratory of the local hospital in the nearby village of Geldrop. This laboratory is involved in a national quality assurance program.

The protocol for the RCT was approved by the medical ethics committee of Maastricht University and the University Hospital Maastricht (the Netherlands).

2.2 The selection procedure

On the basis of the municipal register, all inhabitants of the village born between January 1, 1928 and December 31, 1968 and thus aged 26 to 66 at the time of the RCT, were recorded in the database. These subjects were sent a questionnaire with an accompanying letter, in which the GPs, together with the university, emphasized the need for participation in the selection part of the study, for general health care purposes as well as for the health of the individual patient (t_{-4}; see figure 2.1). This individually addressed information was supported by general information about the study, disseminated via the local press (newspapers and radio).

The questionnaire consisted of six questions regarding the presence or awareness of risk factors for CVD:

1. Do you suffer from a cardiovascular disease?
2. Does your father or mother, or any of your brothers or sisters suffer from a cardiovascular disease, or a high cholesterol level?
3. Do you suffer from diabetes?
4. Do you suffer from hypertension?
5. Is your weight in kg more than your length in cm minus 100?
6. Do you smoke more than five cigarettes a day?

If a person did not return the questionnaire, a reminder was sent, and if necessary he or she was approached by telephone. If one or more of the questions on the returned questionnaire had been answered affirmatively (or undecided), the subject was invited for a further examination at the selection center (t_{-3}).

The examination involved diastolic blood pressure (DBP) and systolic

blood pressure (SBP) measurements, in accordance with the NHG Practice Guideline on Hypertension[1] at the beginning and the end of the visit. In between these measurements, their height and weight were measured, and standardized questions were asked about physical activity (much, little, no exercise in the subject's own opinion) and smoking habits (number of cigarettes per day). A venous blood sample was taken for a total cholesterol (TC) assay. In addition, subjects who were aged between 41 and 66 years were administered the Maastricht Interview on Vital Exhaustion MIVE (at t_{-3}). The MIVE consists of 23 questions, asking about unusual fatigue, loss of energy, increased irritability and feelings of demoralization, all scored as absent or present.[3] Thus, the minimum score was zero, while the maximum score was 23. The duration of one interview was approximately 15 minutes.

All subjects with TC ≥7.0 mmol/l were invited for a second (t_{-2}) and a third visit (t_{-1}). At the second visit, the above procedure was repeated, except for the height measurement and the MIVE assessment. The third visit was similar to the second, except that this time, subjects were asked in advance to fast (i.e., no food or drink, except water, tea, or coffee without cream or sugar, from 10.00 pm the previous evening), since levels of HDL-C, TG, apolipoprotein-A1 (Apo-A1), apolipoprotein-B (Apo-B), lipoprotein(a) (lp(a)) and FB were to be assayed. LDL-C values were calculated using the Friedewald formula. If the TG value was above 4.0 mmol/l, no calculation for LDL-C was made.

TC was measured in accordance with the NHG Practice Guideline on Cholesterol.[2] Three measurements were made within a two-week time span. Persons with a mean TC ≥ 10.0 mmol/l were advized to consult their GP and were excluded from further selection. No particular advice about eating habits or lifestyle was given during the visits.

2.3 Laboratory methods

Blood sampling was done with a vacuum tube system (Becton and Dickinson). Tubes with a gel were used for all parameters, except for FB. Assays were done in serum. Citrated blood (1:10) was used for FB, and the assay was done on plasma.

At the time of blood sampling, the participants were fasting, except

when only TC was sampled. The samples were kept at room temperature and transported for analysis to the nearby hospital laboratory for analysis at the end of every day. Thereafter, the samples were either processed immediately or stored at –30°C.

Laboratory reference values were: TC (4.0-6.5 mmol/l), LDL-C (3.9 – 4.9 mmol/l), HDL-C (male: 0.90 - 1.40 mmol/l; female: 1.20 - 1.60 mmol/l), TG (0.8 – 2.0 mmol/l), Apo-A1 (male: 0.94 - 1,78 g/l; female: 1.01 – 1.98 g/l), Apo-B (male: 0.63 – 1.33 g/l; female: 0.60 – 1.26 g/l) and FB (2.0 – 4.0 g/l). No reference value was available for lp(a), due to the nature of this variable.

The laboratory was participating in the Dutch Foundation for Quality Control in Clinical Hospital Laboratories (SKZL).

2.4 The two cross-sectional studies

The two cross-sectional studies were performed among participants who had an initial TC level -≥ 7.0 mmol/l at the third examination. Their baseline TC level was calculated from the mean of the three TC measurements. Smoking habits and, of course, the other clinical chemical values were assessed at the third examination. Data were statistically processed in SPSS.

2.5 The two prospective studies

Between 1993 and 1995, MIVE was administered during the first examination. Subjects scoring 0-7 on MIVE were labeled as not exhausted, while those scoring 8-23 were labeled as exhausted, in accordance with the instructions.[5] The endpoints for MI and stroke were assessed over a period of approximately six months in 1998, based on data from the GPs' patient records. Endpoint diagnoses were confirmed by a medical specialist. End point definition was taken from the International Classification of Primary Care (ICPC).

The endpoint for MI included the occurrence of nonfatal MI and cardiac death. If a person had experienced more than one event, the first event was used as the endpoint. Survival curves with MI as the dependent variable were constructed for the exhausted and non-exhausted groups.

Covariates such as age, gender, SBP, DBP, TC, body mass index, smoking habits (yes/no), self-reported CVD (Q1) and self-reported diabetes mellitus (Q3 of the questionnaire) were included. Data were entered into SPSS.

Data regarding first stroke were analyzed using continuous vital exhaustion scores. We also used a dichotomous score 'exhausted – not exhausted', using the cut-off point between the 0-7 and 8-23 ranges.[3] The same covariates as for MI were included, except self-reported CVD (Q1) (patient records were inspected to exclude the possibility that vital exhaustion could have been caused by a previous stroke). Data were entered into SPSS.

In the period between the assessment of vital exhaustion and that of the end points, the GPs monitored the subjects by following acknowledged guidelines for cardiovascular risk factors.[1,2]

2.6 The intervention study

Subjects with a mean TC level between 7.0 and 9.9 mmol/l (TC-mean; mean of three measurements) were invited to enter the RCT. At the subjects' first visit to the GP (t_0), it was decided if they were suitable for the RCT. After inclusion, written informed consent was obtained from the subjects. The trial medication, MPPG or placebo, was assigned according to a stratified randomization scheme. On the basis of power calculations (assuming a 20% reduction of TC-mean by MPPG compared to placebo, with a two-sided significance level of 0.05 and a power of 90%), a total of 200 subjects were needed to obtain significant results. Initially, the lower limit was set at 7.5 mmol/l. However, it soon became clear that this limit had to be reduced to 7.0 mmol/l to obtain enough subjects.

The trial medication was a coated tablet with 150 mg MPPG or placebo. The dosage was three tablets per day. Each subject received his medication at the pharmacy on prescription from the GP.

At t_0, the practice-research nurse scheduled appointments with the subjects for blood sampling (at the selection center) and for the consultations with the GP during the follow-up period, i.e., at 1, 3, 6, 9 and 12 months (t_1, t_2, t_3, t_4 and t_4 respectively) (figure 2.1). The procedure for the follow-up visits to the GP was identical to that at the second and third selection visits (except for the blood sampling). At every consulta-

tion, the GP discussed dietary habits and lifestyle with regard to risk factors for CVD (unstandardized) and, if necessary, recommended any improvements he felt were called for.

Once every three months, i.e., at t_2, t_3, t_4 and t_5, treatment compliance was checked by the GP by means of pill counts.

No specific stopping rules were formulated. Termination occurred by the subject's own decision or if the GP estimated this to be in the interest of the subject's health.

Data were entered into SPSS, version 8.0. The analysis was based on intention-to-treat principles. Missing values were replaced by the mean value of the placebo at the corresponding time point, including t_0. Thus, no subjects were removed from the data analysis. Analysis was divided into two parts. The efficacy of MPPG was calculated by comparing the mean values at t_2 in the MPPG group with those in the placebo group, using TC as the primary effect parameter. Secondary effect parameters were LDL-C, HDL-C, TG, Apo-A1, Apo-B, FB and logLp(a), because of skewed distribution. The effectiveness of MPPG was analysed over a period of 12 months. For this purpose, the mean values at t_2, t_3, t_4 and t_5 were combined (t_{2-5}) in the MPPG and the placebo groups. Linear regression analysis was used to check for significant differences in mean values of both efficacy and effectiveness between MPPG and placebo at t_0.

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CHAPTER 3

CHARACTERISTICS OF THE STUDY POPULATION

3.1 Composition of the study population

Subject disposition is summarized in table 3.1. Out of a total of 5894 subjects, 5368 (91%) returned the questionnaire (t_{-4}), of whom 973 subjects answered 'no' to the 6 questions, 292 refused further participation and 13 had moved from the village or died. Thus, 4090 subjects underwent the first examination at the selection center (t_{-3}). Of this subpopulation, 2433 subjects, aged between 41 and 66 years old,

Table 3.1. The Mierlo Project flow chart with the population aged between 26 and 66 years (%).

	SELECTION PART			
t_{-4}	Registered and questionnaire mailed	5894	(100)	
	Unreturned questionnaires	526	(9)	
	Returned questionnaires	5368	(91)	
	All 6 questions 'no'	973	(17)	
	At least one question 'yes'	4395	(75)	
	Refused	2	(5)	
	Moved/died	13	(0)	
t_{-3}	Screened 1x	4090	(69)	
	MIVE subpopulation: 41-66 years	2433	(41)	Studies chapters 6 and 7[1]
	TC < 7.0	3575	(61)	
	No TC measurement available	9	(0)	
t_{-2}	Screened 2x (TC ≥ 7.0 mmol/l)	506	(9)	
	Did not show up	15	(0)	
t_{-1}	Screened 3x (TC ≥ 7.0 mmol/l)	492	(8)	Studies chapter 4 and 5[2]
	TC-mean < 7.0	112	(2)	
	TC-mean ≥ 10.0	2	(0)	
t_0	**INTERVENTION PART**			
	Eligible (7.0 ≤ TC-mean < 10.0)	377	(6)	
	Excluded	116	(2)	
	Refused participation	54	(1)	
	Other reasons	5	(0)	
	Randomized	202	(3)	study chapter 8[3]

TC: total cholesterol (mmol/l); TC-mean: mean value of three measurements at t_{-3}, t_{-2} and t_{-1}.
MIVE: Maastricht Interview Vital Exhaustion

[1] The older part of this population (41 – 66 years) were included in the two prospective studies (chapters 6 and 7).

[2] These subjects were included in the cross-sectional studies of the hypercholesterolemic cohort (chapters 4 and 5).

[3] This population was included in the clinical trial (magnesium-pyridoxal-5'-phosphate-glutamate or placebo) (chapter 8).

underwent the Maastricht Interview on Vital Exhaustion (MIVE; appendix).

Of the 4090 subjects, 3575 persons had a total cholesterol (TC) < 7.0 mmol/l, while TC measurement failed in 9 subjects. Of the subjects with TC ≥ 7.0 mmol/l, 506 participated in the second examination (t_{-2}) and 492 in the third (t_{-1}); 14 subjects either moved, refused further participation, were referred to a specialist or died. The two cross-sectional studies were performed in the 492 subjects remaining at the third examination.

The three measurements were used to calculate TC-mean, which served as the initial TC value at t_0. We found 112 subjects with a TC-mean < 7.0 mmol/l and 2 with a TC-mean ≥ 10.0 mmol/l (these were referred to their general practitioner (GP)), so 377 subjects had a TC-mean between 7.0 and 9.9 mmol/l and were selected to enter the randomized placebo-controlled double-blind intervention trial. In the end, 202 subjects remained for the clinical trial, mainly due to exclusion and refusal.

3.2. Comparison with the general Dutch population

Mierlo is an average Western-European village with approximately 10,000 inhabitants. It is situated in the southern part of the Netherlands, at a distance of 15 km of the town of Eindhoven, which has approximately 200,000 inhabitants. The Mierlo population is originally a rural population, but over the last decades, persons from other places and other backgrounds have settled in the village as well. As such, the Mierlo population may be assumed to have the characteristics of an average, but not representative, West-European population.

Table 3.2 shows a comparison of the gender and age distribution for the general Dutch population[1], the study population (data derived from the municipal register) and the subpopulation that returned the questionnaire (91% of the initial population). Differences between the three populations were minor. Table 3.3 compares the prevalence of hypertension, diabetes mellitus (DM), overweight and smoking among the general Dutch population[2] and the population who returned the questionnaire. Again, differences were minor. Slight differences between the two populations may have resulted from methodological aspects, including the method of questioning, uncertainty with respect to medication (in the case of hypertension) and the difference between body mass index (BMI) and

Table 3.2 Comparison of age and gender distribution in the study population with those in the the general Dutch population (numbers).

Age	general Dutch population		study population		subpopulation who returned the questionnaire	
	Male (x1000)	female (x1000)	male	female	male	female
26-34	15.9 (1352)	15.1 (1284)	10.6 (623)	10.7 (630)	10.8 (580)	11.2 (600)
35-44	14.2 (1209)	13.7 (1166)	18.3 (1078)	18.2 (1073)	16.8 (900)	17.2 (925)
45-54	12.3 (1049)	11.8 (1004)	12.4 (731)	11.2 (661)	12.8 (686)	12.1 (652)
55-66	8.4 (718)	8.6 (735)	9.2 (545)	9.4 (553)	9.3 (500)	9.8 (525)
Total	50.8 (4328)	49.2 (4189)	50.5 (2977)	49.5 (2917)	49.7 (2666)	50.3 (2702)

Table 3.3 Comparison of study population with the general Dutch population in terms of hypertension, weight, smoking habits and diabetes mellitus (% yes; age 26-66 years)

General Dutch population		subpopulation who returned the questionnaire	
Do you have (have you had) hypertension?	7	Do you suffer from hypertension?	10
Do you have (have you had) diabetes?	2	Do you suffer from diabetes?	2
BMI ≥ 25	38	Is your weight in kg more than your length in cm minus 100?	41
More than 5 cigarettes per day	30	Do you smoke more than 5 cigarettes a day?	28

BMI: body mass index (kg/m^2)

'length – 100' (as shorter individuals with relatively higher weight may have 'false' BMI < 25 kg/m^2).

3.3 Composition of study population, stratified by age and gender

Table 3.4 shows the numbers of subjects, divided on the basis of age and gender, in the population derived from the municipal register and the subpopulations at the consecutive steps in the selection procedure. Since we used the Coronary Risk Chart (CRC) to assess the coronary heart disease (CHD) risk and since age in the CRC starts at 30 years, the table includes characteristics of the population aged 30 years and older.

Eight percent of the initial population did not return the questionnaire.

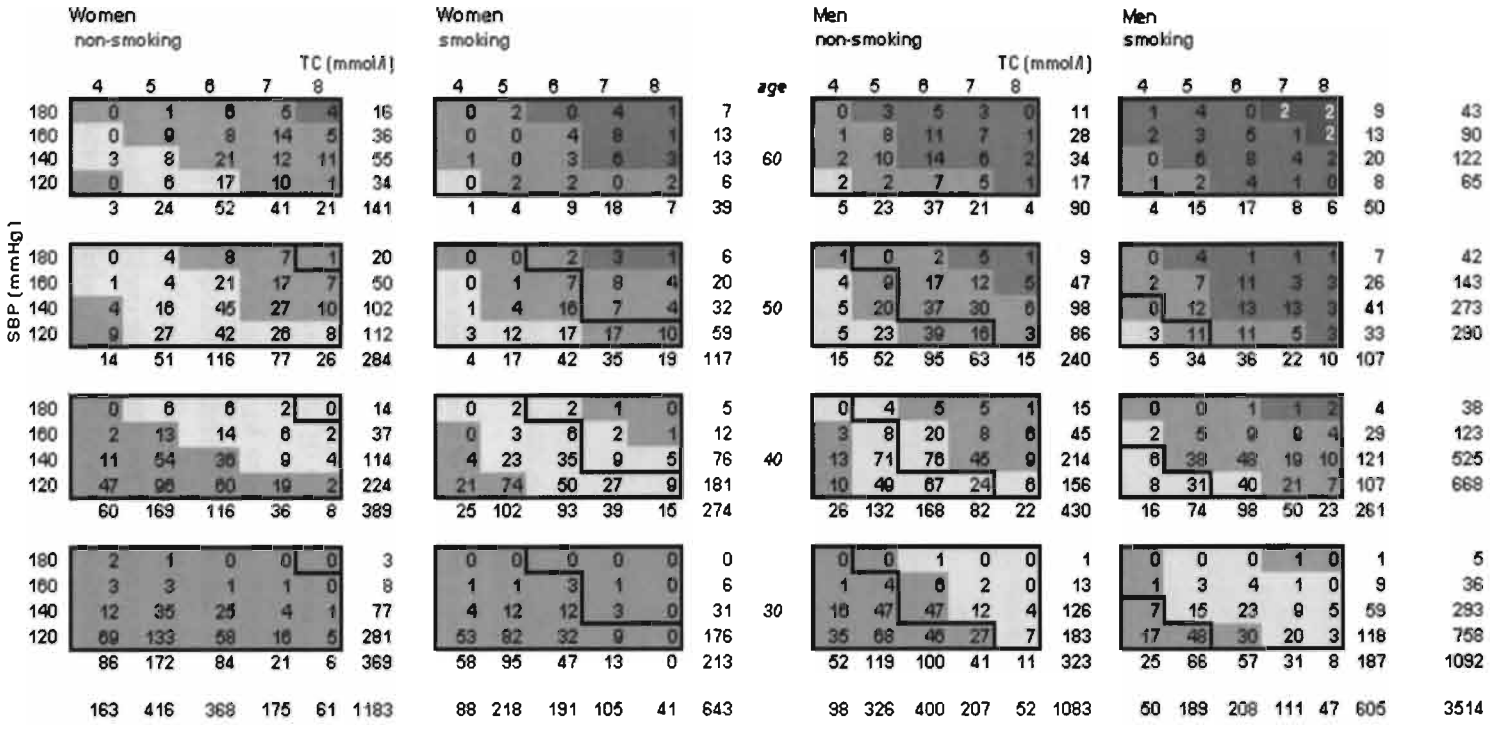
Table 3.4 Numbers of subjects, aged 30 to 66 years, who returned the questionnaire (%), and distribution of answers.

	n	male; 30-49y	male; 50-66y	female; 30-49y	female; 50-66y	
Total population, data derived from municipal register	5458	1899 (35)	865 (16)	1832 (34)	862 (16)	t_{-4}
Subjects who returned questionnaire	5006	1701 (34)	792 (16)	1703 (34)	810 (16)	
Subjects refusing further participation	258	115 (45)	45 (17)	58 (23)	40 (16)	
Subjects having moved/died	13	5 (39)	3 (23)	4 (31)	1 (8)	
All questions answered in the negative	866	332 (38)	107 (12)	331 (38)	96 (11)	
At least one question answered affirmatively and subsequently undergoing examination	3869	1249 (32)	637 (17)	1310 (34)	673 (17)	
'yes' to Q1	250	35 (14)	126 (50)	33 (13)	56 (22)	
'yes' to Q2	2603	793 (30)	392 (15)	931 (36)	487 (19)	
'yes' to Q3	86	6 (7)	35 (41)	12 (14)	33 (38)	
'yes' to Q4	489	119 (24)	128 (26)	105 (21)	137 (28)	
'yes' to Q5	1990	696 (35)	403 (20)	500 (25)	391 (20)	
'yes' to Q6	1289	463 (36)	191 (15)	470 (36)	165 (13)	
Subjects answering Q1 or Q3 affirmatively	320	41 (13)	149 (47)	43 (13)	87 (27)	
Subjects with missing data on TC or BMI	35	6 (17)	1 (3)	21 (60)	7 (20)	
Subpopulation at first examination at selection center*	3514	1201 (34)	487 (14)	1245 (35)	581 (17)	t_{-3}

TC: total cholesterol; BMI: body mass index; y: years; t_{-4} and t_{-3}: see figure 2.1
Questions included in the questionnaire:
Q1. Do you suffer from a cardiovascular disease?
Q2. Does your father or mother, or do any of your brothers or sisters suffer from a cardiovascular disease, or a high cholesterol level?
Q3. Do you suffer from diabetes?
Q4. Do you suffer from hypertension?
Q5. Is your weight in kg more than your length in cm minus 100?
Q6. Do you smoke more than 5 cigarettes a day?
* Not included are subjects answering Q1 or Q3 affirmatively and subjects with missing data on TC or BMI

Further participation was refused by 258 subjects (5%), mainly young males (45%). Thirteen subjects moved or died, while 866 subjects (17%) answered all questions in the negative, indicating that they were not at risk of CHD, and were therefore excluded from further examination.

Figure 3.1. Distribution of subpopulation* at first examination over the *Coronary Risk Chart* (CRC; 4 upper blocks, age 70, not shown).



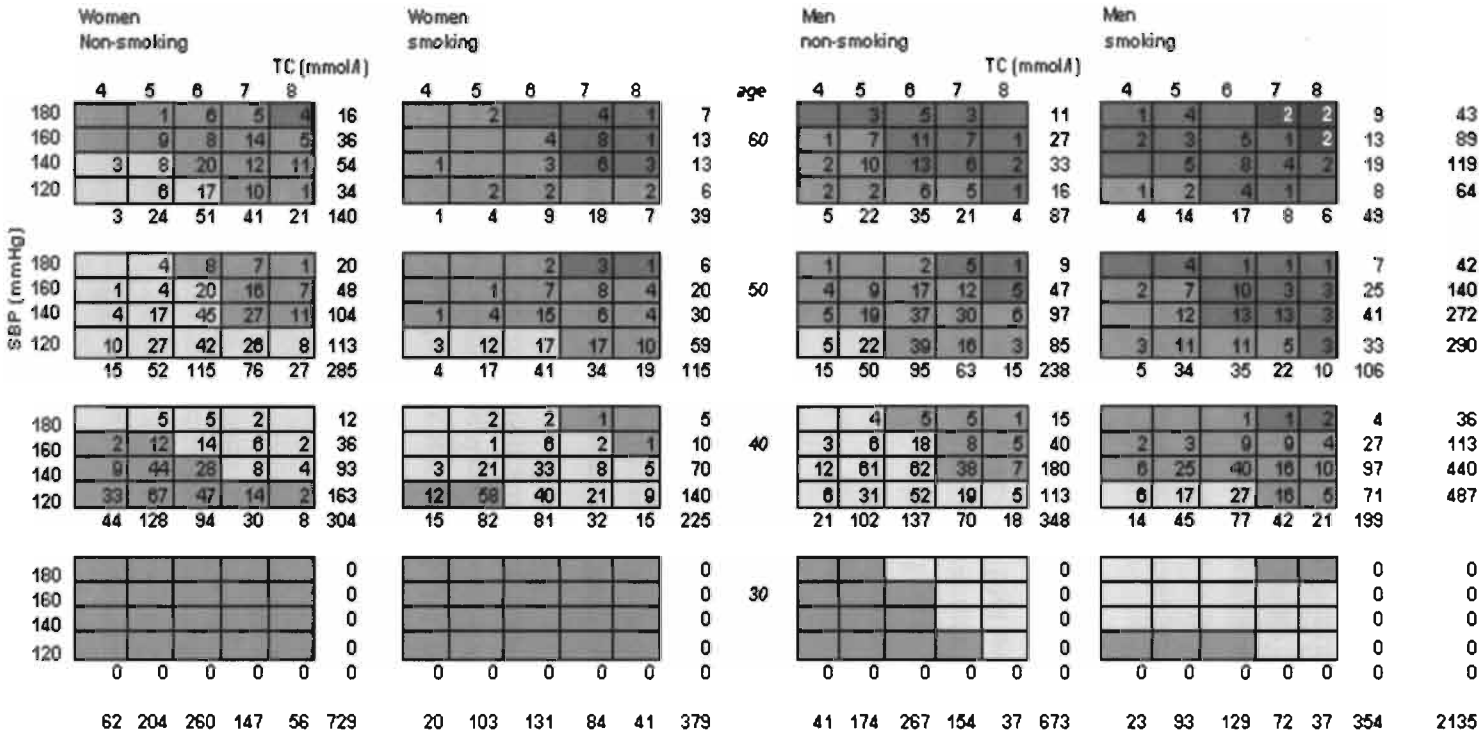
* Not included are subjects answering Q1 or Q3 affirmatively and subjects with missing TC or body mass index data
TC: total cholesterol; SBP: systolic blood pressure

Risk level (% likelihood of coronary event in 10 years)

<5%	5-10%	10-20%	20-40%	>40%	total (%)
1460 (42)	1046 (30)	807 (23)	195 (6)	6 (0)	3510 (100)

shift of 'high risk' border, when projected to age 60, and of value in case of no intervention

Figure 3.2. Distribution of subpopulation undergoing MIVE assessment over the *Coronary Risk Chart* (CRC; 4 upper blocks, age 70, not shown).



* Not included are subjects answering Q1 or Q3 affirmatively and subjects with missing TC data
TC: total cholesterol; SBP: systolic blood pressure

Risk level (% likelihood of coronary event in 10 years)

<5%	5-10%	10-20%	20-40%	>40%	TOT (%)
328 (15)	829 (39)	780 (37)	192 (9)	6 (0)	2135 (100)

This group included a larger percentage of young subjects than the total group who returned the questionnaire (76% aged < 50 years, compared to 68% aged < 50 years in the population who returned the questionnaire). The age distribution in the cohort of subjects who were eventually examined was shifted slightly upwards relative to that in the initial population. The subgroup of subjects who were excluded from the final cohort because they had answered question Q1 or Q3 affirmatively (indicating that they were suffering from cardiovascular disease (CVD) or DM, and therefore not eligible for risk estimation with the CRC) included a relatively large proportion of older men.

Asking subjects about their weight, as Q5 did, produced reliable answers, as we found after comparing these answers with the measurements at the first examination. We observed similar reliability regarding smoking habits (Q6).

The distributions in the subpopulation at the first examination (t_{-3}) hardly showed any deviations from those in the total adult population of Mierlo (t_{-4}) in terms of age and gender.

3.4 CHD risk according the CRC

Table 3.5 lists the characteristics of the subpopulation at the first examination at the selection center (t_{-3}). Blood pressure values were lowest for the younger women, followed by younger men, older women and older men. The highest values for TC and BMI were found in the older female group. For all variables, except for smoking, differences between the younger and older women were much larger than between the younger and older men.

For this subpopulation, variables were available to estimate the cardiovascular risk (likelihood of coronary event in 10 years) using the CRC. Figure 3.1 provides an overview. The distribution of CHD risk is shown in table 3.6, including the numbers of subjects at the various risk levels if no intervention is applied and therefore the distribution over the risk levels is shifted toward the values at the age of 60 years (the shift is illustrated in figure 3.1 by the black lines within the blocks).

Additionally, in view of the nature of the questions in the questionnaire, it may be assumed that the 873 subjects who answered all questions

Table 3.5 Characteristics of cohort* at first examination (t_3) (%).

Number	total	male; 30-49y	male; 50-66y	female; 30-49y	female; 50-66y
Subpopulation at first examination at selection center	3514	1201 (34)	487 (14)	1245 (35)	581 (17)
SBP mean ± SD (mmHg)	132 ± 18	132 ± 14	141 ± 19	124 ± 16	140 ± 21
TC mean ± SD (mmol/l)	5.7 ± 1.1	5.7 ± 1.0	6.0 ± 1.0	5.3 ± 1.0	6.3 ± 1.1
BMI mean ± SD (kg/m²)	25.8 ± 3.7	26.1 ± 3.2	26.7 ± 3.3	24.9 ± 3.9	26.7 ± 4.2
Smoking	1248 (100)	448 (36)	157 (13)	487 (39)	156 (12)

y: years; SBP: systolic blood pressure; TC: total cholesterol; BMI: body mass index; SD: standard deviation; t_3: see figure 2.1
* Not included are subjects answering Q1 or Q3 affirmatively and subjects with missing data on TC or BMI

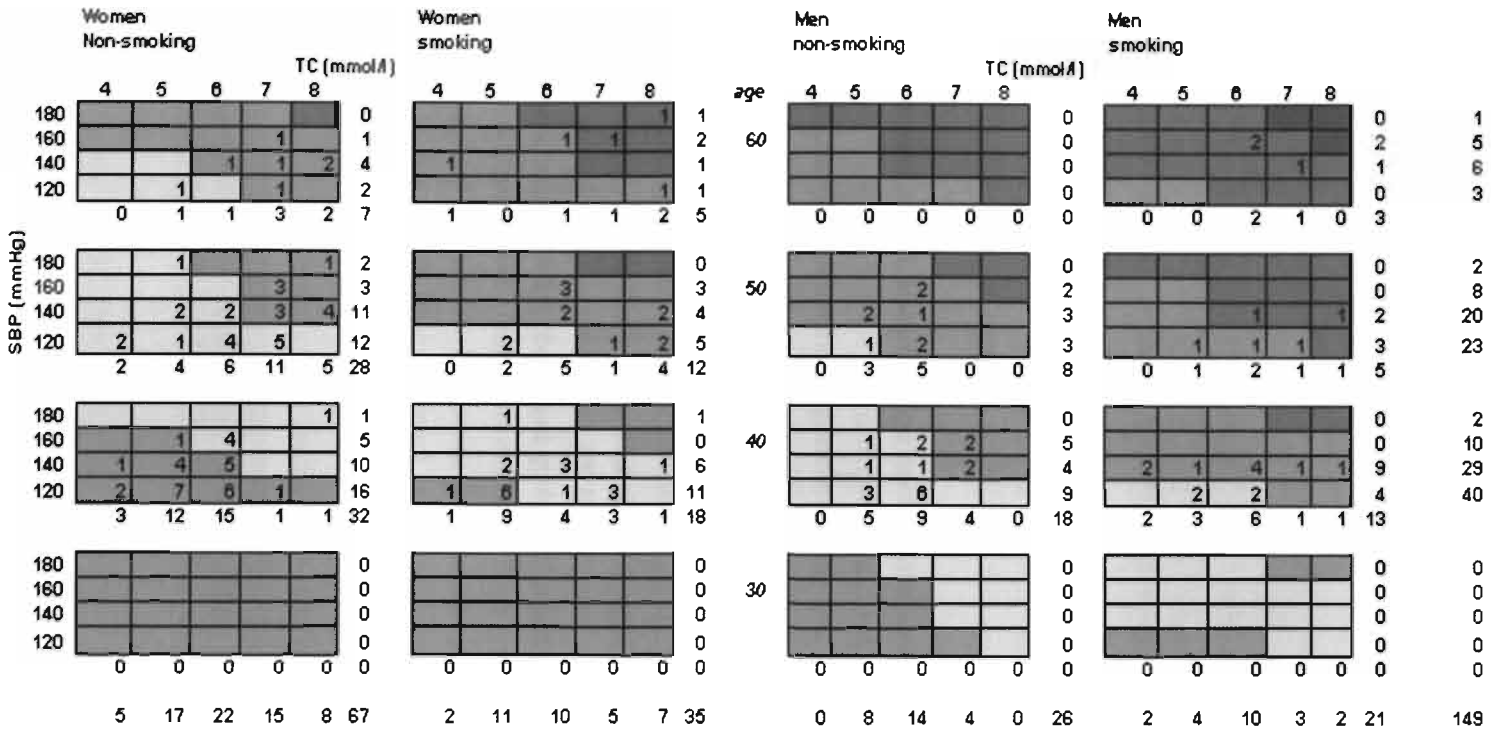
in the negative (and were therefore not included in this subpopulation) were hardly at risk.

Three hundred and thirty-six subjects answered Q1 and Q3 affirmatively, indicating that they were aware of their illness and that they were under treatment by a GP. It may be assumed that the 201 subjects at high or very high risk who were newly found at the first examination in the selection procedure had remained undetected until this study, since they had not answered Q1 or Q3 affirmatively. This group represented 5.7% of the total subpopulation, or 3.7% of the initial population (n=5458). Of these individuals at high or very high risk, 52.7% were smoking men (of whom 97.1% were aged 50 years or older). Assuming the worst case scenario, in which additionally to these 201 subjects at high or very high

Table 3.6 Numbers of subjects at the various risk levels according to the Coronary Risk Chart.

Risk level	number of subjects (%)	number of subjects including those whose risk would – without intervention – shift towards that level at age 60 years (%)
Very high risk; >40%	6 (0)	19 (1)
High risk; 20-40%	195 (6)	968 (28)
Moderate risk; 10-20%	807 (23)	1685 (48)
Mild risk; 5-10%	1046 (30)	717 (20)
Low risk; <5%	1460 (42)	125 (4)

Figure 3.3. Distribution of the vitally exhausted subpopulation over the *Coronary Risk Chart* (CRC; 4 upper blocks, age 70, not shown).



* Not included are subjects answering Q1 or Q3 affirmatively and subjects with missing TC data
TC: total cholesterol; SBP: systolic blood pressure

Risk level (% likelihood of coronary event in 10 years)

<5%	5-10%	10-20%	20-40%	>40%	TOT (%)
34 (23)	55 (37)	53 (35)	7 (5)	0 (0)	149 (100)

risk, the subjects who refused further participation (n=292), those who did not return the questionnaire (n=526) and those who had moved or died (n=13) were also all at high or very high risk, the GPs would have missed a maximum of 18% of the total study population.

3.5 Smoking population

Smoking in itself is a dominant risk factor for CVD, which is reflected in the construction of the CRC. Sixty six percent of the subjects at high or very high risk were smokers, of whom 77% were men. Table 3.7 shows for each age category the percentages of subjects at high or very high risk in the various blocks of the CRC. The differences in percentages between smokers and non-smokers emphasize again the importance of smoking cessation in a population like the Mierlo adult population. This is particularly clear in the older age groups (women, 50-66 y; men, 40-66 y), where the subjects at high or very high risk were exclusively found.

Table 3.7 Percentages of subjects at high or very high risk, according to the Coronary Risk Chart, categorized by smoking and non-smoking, gender and age.

		Percentage of subjects (%)		Percentage of subjects including those whose risk would – without intervention – shift towards that level at age 60 years (%)	
		% non-smoking	% smoking	% non-smoking	% smoking
Women,	60-66 y	3	59	3	59
Women,	50-59 y	0	3	0	25
Women,	40-49 y	0	0	0	7
Women,	30-39 y	0	0	0	2
Men,	60-66 y	59	94	59	94
Men,	50-59 y	5	52	49	87
Men,	40-49 y	0	1	43	83
Men,	30-39 y	0	0	24	61
Women,	50-66 y	1	17	1	33
Men,	40-66 y	8	25	47	85
Total women		0	4	0	1
Total men		6	18	40	78

y = year

Table 3.8 Percentages of subjects per block of the Coronary Risk Chart, for the five TC levels.

	Total cholesterol (mmol/l)					
	n	3.5-4.4	4.5-5.4	5.5-6.4	6.5-7.4	7.5-8.4
F-NS; 60-66 y	141	2	17	37	29	15
F-NS; 50-59 y	284	5	18	41	27	9
F-NS; 40-49 y	389	15	43	30	9	2
F-NS; 30-99 y	369	23	47	23	6	2
F-S; 60-66 y	39	3	10	23	46	18
F-S; 50-59 y	117	3	15	36	30	16
F-S; 40-49 y	274	9	37	34	14	5
F-S; 30-39 y	213	27	45	22	6	0
M-NS; 60-66 y	90	6	26	41	23	4
M-NS; 50-59 y	240	6	22	40	26	6
M-NS; 40-49 y	430	6	31	39	19	5
M-NS; 30-99 y	323	16	37	31	13	3
M-S; 60-66 y	50	8	30	34	16	12
M-S; 50-59 y	290	2	12	12	8	3
M-S; 40-49 y	261	6	28	38	19	9
M-S; 30-39 y	187	13	35	30	17	4

n: number; F: female; M: male; NS: non-smoker; S: smoker; y: year

Projection toward risk calculation at 60 years (assuming no intervention takes place in the subjects at a younger age) resulted in an increased percentage of subjects at high or very high risk, except in the non-smoking female group. This shift increased further with increasing age in both men and women, and, relative to the other groups, in smoking women.

3.6 Hypercholesterolemic population

The selection procedure of the Mierlo Project was used to find hypercholesterolemic subjects. Using the 16 blocks of the CRC, which relate to gender, age and smoking habits, we determined for each block the percentages of subjects for the five TC intervals: 3.5-4.4, 4.5-5.4, 5.5-6.4, 6.5-7.4 and 7.5-8.4 mmol/l (table 3.8). The proportion of hypercholesterolemic subjects was less dependent on age among men than among women. The percentage of subjects with TC ≥ 6.5 mmol/l was largest in the four

CRC blocks for women aged ≥ 50 years, especially those who smoked (64%). This may be due to menopausal aspects.

3.7 Exhausted population

Figure 3.2 shows the distribution of the subpopulation who underwent MIVE assessment, a total of 2135 subjects (eventual MIVE population). Excluded from the original MIVE population (n=2433; aged 41 – 66 years) were subjects who answered Q1 and Q3 affirmatively (indicating that they were suffering from CVD or DM, and therefore not eligible for risk estimation with the CRC) and whose TC values were unknown. Compared to the total sub-population at the first examination (figure 3.1), the percentages of subjects are obviously shifted towards the higher risk estimates, because of the higher age range of this subpopulation, with 9%, against 6% in the total subpopulation, being at high or very high risk. Of the subpopulation regarded as exhausted on the basis of their MIVE scores, 5% were at high risk according to the CRC. This indicates a low correlation between vital exhaustion and CVD risk, calculated on the basis of the standard risk factors used in the CRC (age, gender, smoking habits, SBP, and TC). This is even more evident if one realizes that the CVD risk in the exhausted subpopulation is more prevalent prone among women (68%), younger age (< 50 years) (54%) and non-smokers (62%).

A comparison between the exhausted subpopulation and the total subpopulation of those who underwent MIVE assessment (figures 3.3 and 3.2) shows that, in relative terms, more women than men were exhausted (9% and 5%, respectively), equally distributed among smokers and non-smokers. A slight trend was observed, in both female and male non-smokers, of less vital exhaustion with increasing age (11 to 10 to 5% in women; 5 to 3 to 0% in men). Among female smokers, though not among male smokers, the opposite trend was observed (8 to 10 to 13%).

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2. Health interview survey 1995. Heerlen, Statistics Netherlands (CBS): 1995

CHAPTER 4

RELATIONSHIP BETWEEN SMOKING HABITS AND LOW-DENSITY LIPOPROTEIN-CHOLESTEROL, HIGH-DENSITY LIPOPROTEIN-CHOLESTEROL AND TRIGLYCERIDES IN A HYPERCHOLESTEROLEMIC ADULT COHORT, IN RELATION TO GENDER AND AGE

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4.1 Abstract

Background – Elevated total cholesterol (TC), the related low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and smoking habits are risk factors for cardiovascular disease (CVD).
Objective – To investigate the influence of habitual smoking on LDL-C, HDL-C and TG levels in a hypercholesterolemic population, in relation to gender and age.
Subjects – 492 hypercholesterolemic men and women, aged between 26 and 66 years.
Outcome measures – low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG).
Results – In this hypercholesterolemic cohort, relative differences between smokers and non-smokers in the mean values of TC, LDL-C, HDL-C and TG were 2.2%, 5.5%, -8.1% and 13.7%, respectively. These differences were statistically significant ($p<0.04$).
Over the entire cohort, including men and women, age did not affect the mean values significantly, except for TC and TG values in smoking women, which were significantly higher in women over 50 than in the younger women ($p=0.011$ and $p=0.004$).

In both men and women, regardless of smoking habits, 43 - 59% of the subjects exceeded the upper reference range value for LDL-C (4.9 mmol/l), while 38 - 59% exceeded the upper reference range value for TG (2.0 mmol/l) and 82 - 91% had values below the lower reference range value for HDL-C (0.9 for men; 1.2 mmol/l for women).
Smoking habits hardly influenced the extent to which reference values were exceeded, except for LDL-C in all subjects (higher percentage for smokers; $p=0.041$).
Age gave a similar result, except as regards TG in smoking women, showing high values in 26% of the women < 50 years versus 50% of the women ≥ 50 years ($p=0.026$).
Conclusion – Smoking habits have an adverse effect on LDL-C, HDL-C and TG in a hypercholesterolemic population of both men and women, regardless of age.

4.2 Introduction

Subjects with hypercholesterolemia are at risk of cardiovascular disease (CVD).[1] Related lipemic parameters which are risk factors for CHD are high levels of low density lipoprotein cholesterol (LDL-C)[1] and triglycerides (TG)[2] and low levels of high density lipoprotein cholesterol (HDL-C)[1]. Smoking is another major risk factor.[1]

A study based on an analysis of 54 published studies among adults found a relationship between lipid and lipoprotein concentrations and smoking habits.[3] No such data are available for adult hypercholesterolemic populations.

In 1993, the Mierlo Project was set up in Mierlo, a Dutch village situated 15 km south east of the city of Eindhoven. The entire apparently healthy adult population was screened for CVD risk factors. The Mierlo Project offered a good opportunity to investigate the influence of smoking habits on lipid and lipoprotein values in a hypercholesterolemic population, in relation to gender and age.

4.3 Methods

Design

The Mierlo Project was conducted among the adult population of the Dutch village of Mierlo. It consisted of two intervention studies, one in hypercholesterolemic subjects and one in subjects at cardiovascular risk. Both studies were preceded by a selection procedure, which consisted of a simple questionnaire mailed to inhabitants of the village aged 26 – 66 (birth dates being derived from the municipal register). The six questions concerned the presence of cardiovascular risk factors (heredity, diabetes mellitus (DM), hypertension, overweight, smoking habits, previous cardiovascular disorders). Subjects who answered all questions in the negative were excluded from the study. The other subjects were invited to the health center for a total serum cholesterol measurement. Measurements were performed according to the guidelines of the Dutch College of General Practitioners (NHG).[4] Smoking habits (number of cigarettes per day) were asked for.

Participants with total cholesterol levels ≥ 7.0 mmol/l were invited for a second and a third visit within a period of two months, for two additional cholesterol measurements. At the third visit, the subjects had to be fasted, since HDL-C and TG were also assayed. LDL-C values were calculated with the Friedewald equation. If the TG value was above 4.00 mmol/l, the LDL-C value was not calculated.

During the visits, no particular recommendations were given as to eating habits or lifestyle. Medication was not recorded. The visits took place between May 1993 and May 1995.

Laboratory methods

Blood was sampled with a vacuum tube system (Becton and Dickinson), tubes with a gel being used for all parameters. Assays were done in serum. The samples were kept at room temperature and transported for analysis to the nearby hospital laboratory at the end of every day for analysis. There after, the samples were either processed immediately or stored at –30°C.

TC Assays used Boehringer's CHOD-PAP method on a Hitachi 911, while TG assays used a Boehringer enzymatic method on a Hitachi 911, without correction for glycerol, and HDL-C was measured with Instrumentation Laboratory's CHOD-PAP method on a Instrumentation Laboratory Monarch analyzer, after precipitation with PEG/dextrane sulphate/Mg).

The reference rangesused at the laboratory were 4.00-6.50 mmol/l for TC, 3.90-4.90 mmol/l for LDL-C, 0.90-1.40 mmol/l (for men) and 1.20-1.60 mol/l (for women) for HDL-C, and 0.80-2.00 mmol/l for TG.

The laboratory was involved in a national quality assurance program.

Statistical analysis

Data were entered into SPSS, version 9.0. Differences in risk factors between subpopulations were compared using Fisher's Exact Test as a chi-square test, while an independent t-test was used in the case of normal distribution, together with Levine's Test for Equality of Variances as an F-test. All p-values were two-sided.

4.4 Results

The results of the selection procedure are summarized in table 4.1. A total number of 4090 subjects underwent the first examination at the health center. Mean TC level was 5.68 mmol/l (4081 persons; 9 missing TC measurements). Subsequently, 506 subjects with TC values of at least 7.0 mmol/l participated in the second examination and 492 in the third. These formed our cohort. For each subject, the mean of these three measurements was calculated. This meant that the TC levels of some subjects in our hypercholesterolemic cohort sank to below 7.0 mmol/l, as a consequence of the phenomenon of regression to the mean. The mean TC level of our hypercholesterolemic cohort was 7.35 mmol/l. Table 4.2 shows the baseline characteristics. The older women had significantly higher mean TC and TG values than the younger group.

Table 4.1. Results of the selection process (%).

Registered	5894	(100)
Unreturned questionnaires	526	(9)
Returned questionnaires	5368	(91)
All questions 'no'	973	(17)
At least one question 'yes'	4395	(75)
Refused	292	(5)
Moved/died	13	(0)
Screened 1x	4090	(69)
TC<7.0	3575	(61)
No TC measurement available	9	(0)
Screened 2x	506	(9)
Did not show up	14	(0)
Screened 3x	492	(8)

Table 4.2. Baseline characteristics of subjects.

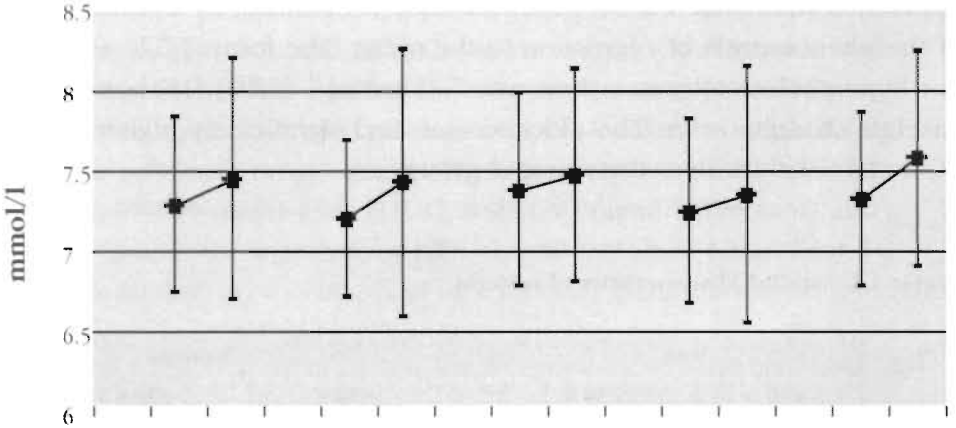
	Men							Women						
	<50 y			≥50 y				<50 y			≥50 y			
	n	mean	SD	n	mean	SD	p	n	mean	SD	n	mean	SD	p
TC	156	7.30	0.73	105	7.29	0.52	0.830	78	7.28	0.58	153	7.47	0.64	0.028
LDL-C	144	4.90	0.84	99	4.87	0.74	0.791	78	4.76	0.87	148	4.79	0.90	0.792
HDL-C	155	1.23	0.34	105	1.30	0.42	0.195	78	1.67	0.51	153	1.60	0.45	0.294
TG	155	2.59	1.76	105	2.46	1.56	0.547	78	1.78	0.91	153	2.17	1.20	0.013

n: number; y: year; TC: total cholesterol (mmol/l); LDL-C: low density lipoprotein cholesterol (mmol/l); HDL-C: high density lipoprotein cholesterol (mmol/l); TG: triglycerides (mmol/l)

All mean values (TC, LDL-C, HDL-C and TG) were significantly more unfavorable for smokers than for non-smokers (figure 4.1-4.4). The relative differences in mean TC, LDL-C, HDL-C and TG values between smokers and non-smokers were 2.2%, 5.5%, -8.1% and 13.7%, respectively. These significant differences were mainly caused by the men, and were not seen in the women, except for HDL-C (p=0.042). The age subgroups (<50 vs. ≥50 years) showed similar differences between smokers and non-smokers for LDL-C, HDL-C and TG, though some of the differences were not significant.

Dividing the population into the four subgroups, based on age and gender (men<50 y, men≥50 y; women<50 y; women≥50 y), values for mean TC levels were significant higher for smokers versus non-smokers in the older male group and older female group (resp. p=0.004 and 0.039; not shown). Mean LDL-C was significant higher for smokers in the younger male group (p=0.013), whereas HDL-C was significant lower for

Figure 4.1. Mean TC ± SD values and significance of the difference between smokers and non-smokers in the total cohort, including men as well as women, and younger age category (<50y) as well as older category (≥50y).



	NS-all	S-all	NS-men	S-men	NS-fem	S-fem	NS<50	S<50	NS≥50	S≥50
n	302	189	156	104	146	85	123	110	179	79
mean	7.29	7.45	7.2	7.43	7.38	7.47	7.25	7.35	7.32	7.58
SD	0.55	0.75	0.49	0.83	0.6	0.66	0.57	0.8	0.54	0.67
p		0.012		0.012		0.301		0.233		0.003

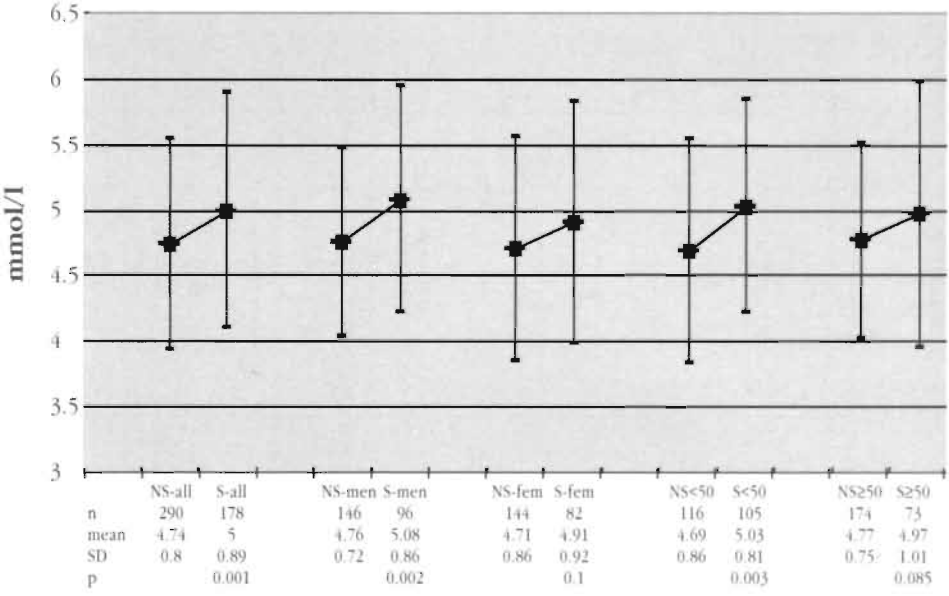
TC: total cholesterol (mmol/l); NS: non-smokers; S: smokers; fem: female; SD: standard deviation; p: significance

smokers in the younger female group (p=0.047). In these four subgroups all other measured variables did not show significances between smokers and non-smokers.

In smokers, mean TC level was significant higher in the older population, compared to the young subjects (7.58 and 7.35 mmol/l; p=0.042). In non-smokers this effect was not demonstrated. Dividing the population into smoking men, smoking women, non-smoking men and non-smoking women, considering young versus old, yielded no significant differences in mean values, except for the mean TC and TG values in the female smoking group. These values were significantly higher among smoking women over 50 than in the younger group (p = 0.011 and 0.004, respectively).

Table 4.3 shows that a larger percentage of subjects (> 80%) exceeded the reference value for HDL-C than those for LDL-C and TG. In general, a larger percentage of men than of women exceeded the upper

Figure 4.2. Mean LDL-C ± SD values and significance of difference between smokers and non-smokers in the total cohort, including men as well as women, and younger age category (<50y) as well as older category (≥50y).



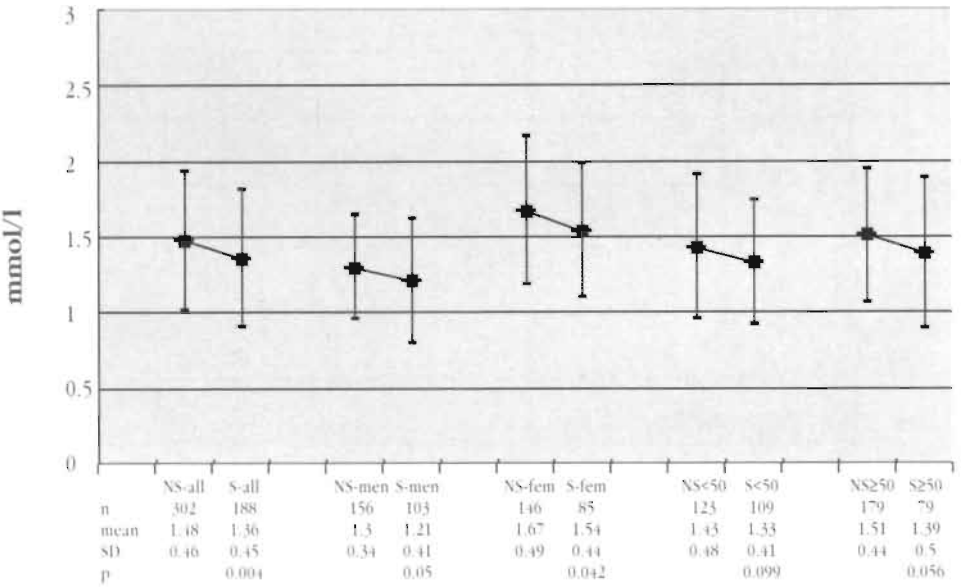
LDL-C: low density lipoprotein cholesterol (mmol/l); NS: non-smokers; S: smokers; fem: female; SD: standard deviation; p: significance

Table 4.3. Proportions of subjects (%) among smokers and non-smokers with values exceeding reference values.

	Non-smokers		smokers		
LDL-C (mmol/l)	**n**	**n-exceeding**	**n**	**n-exceeding**	**p**
Total	302	147 (49)	189	108 (57)	0,041
Men	156	84 (54)	104	61 (59)	0,262
Women	146	63 (43)	85	47 (55)	0,078
HDL-C (mmol/l)					
total	302	261 (86)	189	157 (83)	0,187
men	156	142 (91)	104	87 (84)	0,081
women	146	119 (82)	85	70 (82)	1,000
TG (mmol/l)					
total	302	140 (46)	189	93 (49)	0,301
men	156	78 (50)	104	61 (59)	0,205
women	146	62 (42)	85	32 (38)	0,491

Abbreviations and reference values. LDL-C: low density lipoprotein cholesterol (4.9 mmol/l); HDL-C: high density lipoprotein cholesterol (men: 0.9 mmol/l; women 1.2 mol/l); TG: triglycerides (2.0 mmol/l)

Figure 4.3. Mean HDL-C ± SD values and significance of difference between smokers and non-smokers in the total cohort, including men as well as women, and younger age category (<50y) as well as older category (≥50y).

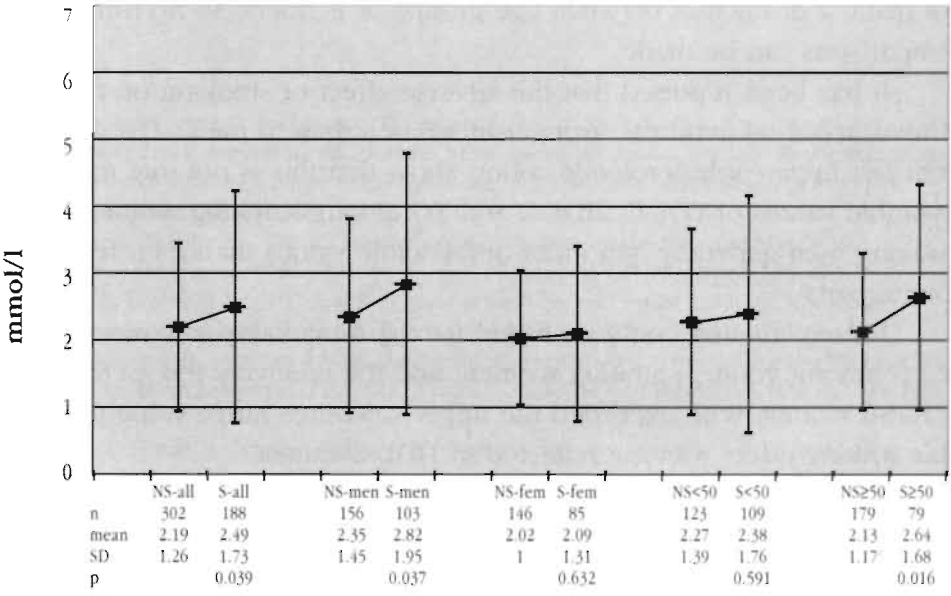


HDL-C: high density lipoprotein cholesterol (mmol/l); NS: non-smokers; S: smokers; fem: female; SD: standard deviation; p: significance

reference range values for the three parameters. No significant differences between smokers and non-smokers were observed with regard to the percentages of subjects exceeding the reference values for HDL-C (<0.9 for men; < 1.2 mmol/l for women) or TG (> 2.0 mmol/l), though there was a significant difference for LDL-C in all subjects (p=0.041). This significant value may be more attributable to women than to men.

In agreement with the findings for the mean values, age (<50 vs. ≥50 years) did not significantly affect the differences in the percentages exceeding reference values, except for TG in smoking women, where the percentages were 26% in the younger population versus 50% in the older group (p=0.026) (not shown). This may be attributed to the small proportion of smoking women < 50 years who exceeded the TG reference value (26%), compared to the percentages for non-smoking women < 50 years (49%) and ≥ 50 years (41%) and for smoking women ≥50 years (50%). The difference between the younger smoking and non-smoking

Figure 4.4. Mean TG ± SD values and significance of difference between smokers and non-smokers in the total cohort, including men as well as women, and younger age category (<50y) as well as older category (≥50y).



TG: triglycerides (mmol/l); NS: non-smokers; S: smokers; M: fem: female; SD: standard deviation; p: significance

women showed a trend towards significance (p=0.057). No significant results were observed for LDL-C or TG.

4.5 Discussion

Our study of a hypercholesterolemic cohort showed significantly higher mean values of LDL-C and TG, and a significantly lower mean value of HDL-C in smokers compared to non-smokers. The overall values for our hypercholesterolemic group were more unfavorable than those of an average adult population reported by a previous review analyzing 54 published studies.[3] The difference in LDL-C values between smokers and non-smokers in our cohort was 5.5%, compared to 1.7% in the review, while the difference in HDL-C values in our cohort was –8.1%, compared to –5.7% in the review, and the difference in TG values in our cohort was 13.7%, compared to 9.1% in the review. The review found a significant dose-response effect (non-smokers, light, moderate, and heavy smokers) for the lipid values. Since our smokers group included light smokers (all subjects > 0 cigarettes), the actual difference in percentages between the two studies may be even more substantial. The review did not make a distinction between age groups or genders, so no further comparisons can be made.

It has been reported that the adverse effect of smoking on the risk of myocardial infarction is stronger in women than in men.[5] The data from our hypercholesterolemic cohort show that this is not due to less favorable values of LDL-C, HDL-C and TG among smoking women, since smoking men generally had more unfavorable values than their female counterparts.

No explanation could be found for the remarkably low mean value of TG among young, smoking women, and the relatively low percentage of these women who exceeded the upper reference range value for TG. This striking effect was not reflected in HDL-C values.

Smoking enhances the development of atherosclerosis. The effect may be exerted directly on the artery walls, or be mediated by altered blood coagulation, increased homocysteine levels or increased lipid and lipoprotein levels in the blood. A dose response effect has been found between smoking habits and lipid and lipoprotein parameters, which

supports the view that there may be a causal relationship.3 This relation is also supported by the results of many studies showing that lipid and lipoprotein concentrations in ex-smokers are either the same as those found in non-smokers or are intermediate between concentrations in smokers and non-smokers.[3] The causal relation may be due to a direct effect (altered appetite and taste) or to altered dietary habits, since smokers tend to eat less fruit and vegetables and more fat.[6-8] Our findings, which show less favorable mean LDL-C, HDL-C and TG values in our hypercholesterolemic cohort than in the average population, do not contradict this idea of a causal relationship.

In conclusion, smoking is not only a CVD risk factor as such, but in a hypercholesterolemic population, it may increase the CVD risk even more through its adverse influence on LDL-C, HDL-C and TG levels. It may be concluded that non-smoking seems to reduce lipid and lipoprotein risk factors, which may be an encouragement to stop smoking. Since it has been established that CVD risk decreases more rapidly in patients with established coronary heart disease after they stop smoking than in asymptomatic subjects[1], stopping smoking may be even more effective in reducing CVD risk in hypercholesterolemic men and women, of all ages, than in normocholesterolemic subjects.

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CHAPTER 5

FIBRINOGEN LEVELS IN SMOKING AND NON-SMOKING HYPERCHOLESTEROLEMIC INDIVIDUALS IN RELATION TO AGE AND GENDER

Accepted for publication in Clinical and Experimental Medicine. Schuitemaker GE, Dinant GJ, van der Pol GA, van Wersch JWJ. Fibrinogen levels in smoking and non-smoking hypercholesterolemic individuals in relation to age and gender.

5.1 Abstract

Background – Elevated total cholesterol (TC) and plasma fibrinogen (FB) levels and smoking are risk factors for cardiovascular disease (CVD), whose interrelationships and effect on CVD risk are influenced by both gender and age.

Objective – To investigate the effect of smoking on FB levels in a hypercholesterolemic population subdivided on the basis of gender and age.

Subjects – 492 hypercholesterolemic subjects, divided into four subpopulations: men and women, aged 26-49 and 50-66 years.

Results – Mean fibrinogen levels among smokers and non-smokers in the four subpopulations of this hypercholesterolemic cohort followed mean total cholesterol levels. Three subpopulations (men < 50y, men ≥ 50 y and women ≥ 50 y) showed differences in mean total cholesterol and fibrinogen values between smokers and non-smokers: total cholesterol 7.23 ± 0.54 vs. 7.40 ± 0.93 mmol/l and fibrinogen 2.79 ± 0.48 vs. 3.23 ± 0.72 g/l in men <50 y; total cholesterol 7.17 ± 0.43 vs. 7.50 ± 0.60 mmol/l and fibrinogen 3.11 ± 0.44 vs. 3.68 ± 0.66 g/l in men ≥50 y and 7.41 ± 0.59 vs. 7.65 ± 0.73 mmol/l and fibrinogen 3.29 ± 0.61 vs. 3.58 ± 0.71 g/l in women ≥ 50 y. These values correspond with the percentage difference between smokers and non-smokers in total cholesterol and fibrinogen of 2.4 and 15.8% (men, <50 y), 4.6 and 18.3% in men ≥50 y and 3.2 and 8.8% in women ≥50 y. All differences were significant ($p<0.05$), except for total cholesterol in the younger men (< 50 y). No differences between smokers and non-smokers were observed in the younger female group (< 50 y).

Except in the younger female group (< 50 y), significant differences between smokers and non-smokers were also observed in the number of subjects exceeding the upper reference value of fibrinogen (> 4.0 g/l), the highest percentage being found for the smoking older women (≥ 50 y) (29%).

Conclusion – Smoking elevates FB levels in hypercholesterolemic men (< 50 y; ≥ 50 y) and older women (≥ 50 y), but not in younger women (< 50 y).

5.2 Introduction

Subjects with hypercholesterolemia and smokers are at risk of coronary heart disease (CHD). The risk increases with advancing age, and men are more at risk than women. All this is shown by the abundant data available on this subject.[1] Additionally, elevated FB levels are nowadays considered to be an independent risk factor, not only for CHD[1-3] but also for stroke[4-8], diabetes[9], peripheral vascular disease[10], non-arteritic anterior ischemic optic neuropathy[11] and poor periodontal status.[12] Little is known about the interrelationship between FB and smoking in relation to both gender and age in a hypercholesterolemic population. This relation is socially relevant for CVD risk, especially in women, since habitual smoking has become more frequent among women.[13] The combination with the age factor is interesting because of the difference in risk between premenopausal women and postmenopausal women. The literature provides one study that reported about the relationship between FB and smoking using a subdivision into four subgroups based on gender and age (the second MONICA Augsburg survey).[14] The study was performed in an average population.

The Mierlo Project was set up in the Dutch village of Mierlo, situated 15 km south-east of the city of Eindhoven. A screening procedure was performed in the entire apparently healthy adult population to select subjects with hypercholesterolemia for a clinical trial. The Mierlo Project offered a good opportunity to investigate the influence of smoking on FB values in a hypercholesterolemic population, in relation to gender and age.

5.3 Methods

Design

The Mierlo Project was conducted among the adult population of the Dutch village of Mierlo. It consisted of two intervention studies, one in hypercholesterolemic subjects and one in subjects at cardiovascular risk. Both studies were preceded by a selection procedure, which consisted of a simple questionnaire mailed to those inhabitants of the village aged 26 – 66 (birth dates being derived from the municipal register). The six

questions concerned the presence of cardiovascular risk factors (heredity, diabetes mellitus (DM), hypertension, overweight, smoking, previous cardiovascular disorders). Subjects who answered all questions in the negative were excluded from the study. The other subjects were invited to the health center for a total serum cholesterol measurement. Measurements were performed according to the Practice Guideline of the Dutch College of General Practitioners (NHG).[15] Smoking habits (in terms of numbers of cigarettes per day) were also asked for.

Participants with total cholesterol levels ≥ 7.0 mmol/l were invited for a second and third visit within a period of two months, for two additional cholesterol measurements. At the third visit, FB was also assayed.

During the visits, no particular recommendations were given as to eating habits or lifestyle. Medication was not recorded.

Laboratory methods

Blood was sampled with a vacuum tube system (Becton and Dickinson), using tubes with a gel. The samples were kept at room temperature and transported for analysis to the nearby hospital laboratory at the end of each day for analysis. Thereafter, the samples were either processed immediately or stored at –30°C.

Assay for TC was done in serum using Boehringer's CHOD-PAP method on a Hitachi 911. FB was measured in citrated blood (1:10). The assay was done on plasma with thrombin according to the Clauss method on the Boehringer STA compact analyser. The reference ranges used at the laboratory were 4.00-6.50 mmol/l for TC and 2.00-4.00 g/l for FB.

The laboratory was involved in a national quality assurance program.

Statistical analysis

Data were processed in SPSS, version 9.0. Differences in risk factors between subpopulations were compared using Fisher's Exact Test as a chi-square test, while an independent t-test was used in the case of normal distribution, together with Levine's Test for Equality of Variances as an F-test. All p-values were two-sided.

5.4 Results

The results of the selection procedure are summarized in table 5.1. A total number of 4090 subjects underwent the first examination at the health center. Mean TC level was 5.68 mmol/l (4081 persons; 9 missing TC measurements). Subsequently, 506 subjects with TC values of at least 7.0 mmol/l participated in the second examination and 492 in the third. These formed our cohort. For each subject, the mean of the three measurements was calculated, which meant that the TC levels of some subjects in our hypercholesterolemic cohort sank to below 7.0 mmol/l, as a consequence of the phenomenon of regression to the mean. The mean TC level of our hypercholesterolemic cohort was 7.35 mmol/l.

Table 5.1. Results of the selection process (%).

Registered	5894	(100)
Unreturned questionnaires	526	(9)
Returned questionnaires	5368	(91)
All questions 'no'	973	(17)
At least one question 'yes'	4395	(75)
Refused	292	(5)
Moved/died	13	(0)
Screened 1x	4090	(69)
TC<7.0	3575	(61)
No TC measurement available	9	(0)
Screened 2x	506	(9)
Did not show up	14	(0)
Screened 3x	492	(8)

Table 5.2 shows the baseline characteristics. The older women (≥ 50 y) had significantly higher mean TC values than the younger group (< 50 y). In both genders, the older groups (≥ 50 y) had significantly higher FB levels than the younger groups. In both age groups (<50; ≥50 y), mean FB levels were higher for women than for men.

Table 5.2. Baseline characteristics of subjects.

	Men							women						
	<50 y			≥50 y				<50 y			≥50 y			
	n	mean	SD	n	mean	SD	p	n	mean	SD	n	mean	SD	P
TC	156	7.30	0.73	105	7.29	0.52	0.830	78	7.28	0.58	153	7.47	0.64	0.028
FB	156	2.98	0.63	105	3.31	0.59	0.000	77	3.10	0.60	153	3.37	0.65	0.003

n: number; y: year TC: total cholesterol (mmol/l); FB: fibrinogen (g/l)

Within the four subgroups, differences in mean FB levels between smokers and non-smokers showed a similar pattern as differences in mean TC levels (see figures 5.1 and 5.2). In percentage terms, the differences in mean values between smokers and non-smokers were much higher for FB than for TC; this was true for all four subgroups (table 5.3). All TC and FB values were significantly higher in the smoking subgroups, except in the younger female group (< 50 y), which showed minor differences for both TC and FB, and in the younger male group (< 50 y), with minor differences for TC.

Table 5.3. Percentage differences in mean TC and FB values between non-smokers and smokers (smokers having higher mean values) and ratio between FB and TC in men (<50; ≥50 y) and women (<50; ≥50 y).

	men		women	
	<50 y	≥50 y	<50 y	≥50 y
TC	2.4	4.6*	0.1	3.2*
FB	15.8*	18.3*	0.6	8.8*
FB/TC	6.6	4.0	6.0	2.8

y: year; TC: total cholesterol; FB: fibrinogen; *: p<0.05

Table 5.4 shows that in three subpopulations, a significantly higher percentage of smokers than non-smokers exceeded the upper reference range value of FB, while the group of younger women (< 50 y) showed the opposite relationship. In this subgroup, 20% percent of the non-smokers exceeded the upper reference value, against 9% of the smoking women. This difference was not significant.

Table 5.4. Proportions of subjects (%) among smokers and non-smokers with values exceeding reference values.

	Non-smokers		smokers		
FB (g/l)	**n**	**n-exceeding**	**n**	**n-exceeding**	**p**
total	302	27 (9)	189	34 (18)	0.005
men < 50 y	88	2 (2)	67	8 (12)	0.020
men ≥ 50 y	68	4 (6)	37	10 (27)	0.005
women < 50 y	35	7 (20)	43	4 (9)	0.206
women ≥ 50 y	111	14 (13)	42	12 (29)	0.029

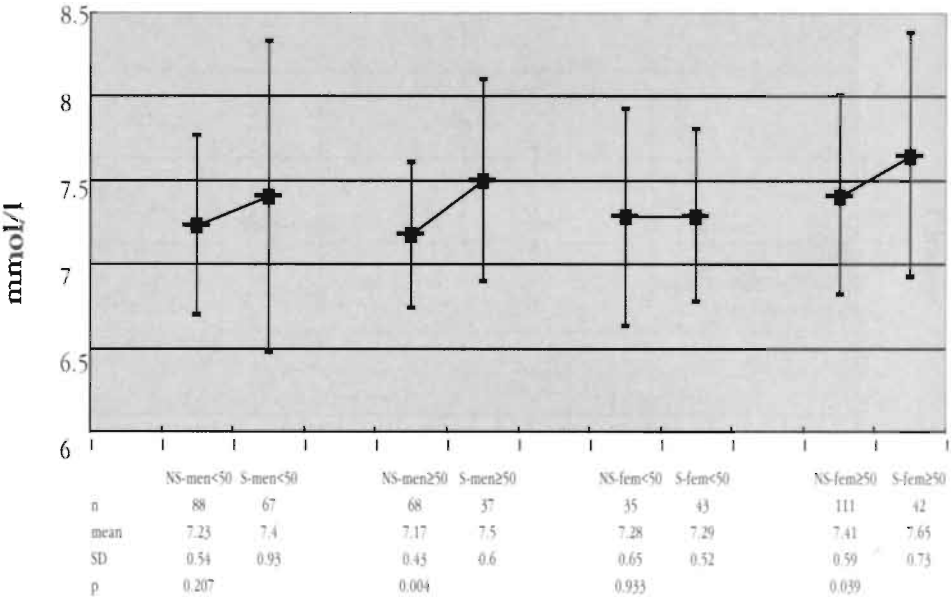
y: year; TC: total cholesterol; FB: fibrinogen; *: p<0.05

5.5 Discussion

Our results concern a hypercholesterolemic population. It is known from studies in normocholesterolemic populations that fibrinogen levels among smokers are higher than those among non-smokers.[14,16,17] This was also observed in our study in three of the hypercholesterolemic subpopulations, namely those including men <50 years, men ≥ 50 years and women ≥ 50 years. Mean fibrinogen levels per age category were higher in women than in men (table 5.2). Fibrinogen levels increased with age.

An exception to this pattern was our finding in the fourth subpopulation, the younger female subpopulation (< 50 y), in which the smokers had markedly low fibrinogen levels. Moreover, the percentage of subjects exceeding the upper reference value was relatively low (9%) among the smokers in this subpopulation and relatively high among non-smokers (20%).

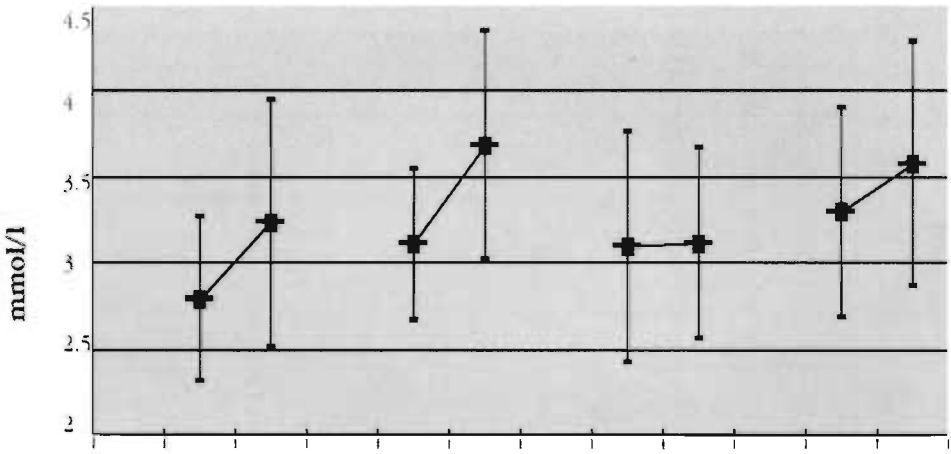
Figure 5.1. Mean TC ± SD values and significance of the difference between smokers and non-smokers in four subgroups: men <50y), men ≥50y, women <50 y and women ≥50 y.



TC: total cholesterol (mmol/l); NS: non-smokers; S: smokers; fem: female; SD: standaard deviation; p: significance

These percentages were also high compared to those in the three other subgroups (table 4). Evidently, we looked for an explanation for this phenomenon, especially since it is known that this subgroup is at very low risk of CVD. Looking at the numbers of cigarettes smoked in each subgroup did not provide an explanation, since the percentage of women in the younger group who smoked 10 to 19 cigarettes per day was higher than that in the older group (47 versus 33%), whereas more of the older women smoked 5 to 9 cigarettes per day (19 versus 7%). Other possible explanations include the number of smoking years or whether subjects inhaled or not. However, we have no data on these topics. Nor do we have data on other covariates that may act as confounders in this unexpected outcome among the group of smoking women aged < 50y, like the use of oral contraception and medication, alcohol consumption, fibrinogen polymorphism, estrogen levels (since we took 50 years as the cutoff point), and the menstrual cycle, all of which may

Figure 5.2. Mean FB ± SD values and significance of the difference between smokers and non-smokers in four subgroups: men <50y), men ≥50y, women <50 y and women ≥50 y.



	NS-men<50	S-men<50	NS-men≥50	S-men≥50	NS-fem<50	S-fem<50	NS-fem≥50	S-fem≥50
n	88	67	68	37	34	43	111	42
mean	2.79	3.23	3.11	3.68	3.09	3.11	3.29	3.58
SD	0.48	0.72	0.44	0.66	0.67	0.55	0.61	0.71
p	0.000		0.000		0.867		0.012	

FB: fibrinogen (g/l); NS: non-smokers; S: smokers fem: female; SD: standaard deviation; p: significance

interfere with fibrinogen levels. Information on these variables might have helped us find a more satisfactory explanation. Furthermore, we should mention that, as has been found in many other studies, fibrinogen measurements are difficult to standardize and are subject to biological variations. Finally, the present study was conducted before the introduction of the lipid lowering HMG CoA reductase inhibitors.

A similar unexpected result for the same smoking female subpopulation (<50 y) was found in an earlier study on the Mierlo Project, assessing the effect of the mean triglyceride level in the same young female group.[18] This level was found to be 12% lower among smoking women than among non-smoking women, although the difference was not significant (p=0.274). On the other hand, mean LDL-cholesterol and mean HDL-cholesterol levels within the same population gave the expected results, with LDL-cholesterol being 8.4% higher (p=0.073) and HDL-cholesterol being 12.8% lower among smokers (p=0.047). Like the current findings on fibrinogen, we were not able to find an explanation for these findings.

In conclusion, we found similar patterns for mean total cholesterol and fibrinogen levels in all four subpopulations in relation to smoking. The effect on fibrinogen was much stronger than on total cholesterol. Smoking may be a risk factor for CHD, also by exerting an effect on fibrinogen.

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CHAPTER 6

ASSESSMENT OF VITAL EXHAUSTION CONTRIBUTES TO THE IDENTIFICATION OF SUBJECTS AT INCREASED RISK OF MYOCARDIAL INFARCTION IN GENERAL PRACTICE

Accepted for publication in Psychosomatics. Schuitemaker GE, Dinant GJ, van der Pol GA, Appels A. Assessment of vital exhaustion contributes to the identification of subjects at increased risk of myocardial infarction in general practice.

6.1 Abstract

Background – Vital exhaustion (VE), a state characterized by unusual fatigue, loss of energy, increased irritability and feelings of demoralization, is one of the cardiovascular risk factors.
Objective – To investigate whether vital exhaustion (VE) contributes to the identification of subjects at increased risk of myocardial infarction (MI) in general practice.
Design – Prospective cohort study.
Method – VE was assessed with the Maastricht Interview on Vital Exhaustion (MIVE). Other cardiovascular risk factors established were age, gender, systolic and diastolic blood pressure (SBP and DBP), total cholesterol (TC), body mass index (BMI), smoking habits, cardiovascular disease (CVD) and diabetes mellitus (DM). A Cox regression analysis was used.
Subjects – Adults (41 – 66 years) in an average Dutch village population.
Outcome measures – Fatal and non-fatal myocardial infarction.
Results –At the univariate level, VE doubled the risk of MI (RR=2.54; 95% CI 0.97-6.64). The effect of exhaustion was confounded by gender, women having higher exhaustion scores and a lower incidence of MI. Controlling for gender, age, SBP, TC, smoking habits, self-reported CVD and DM, VE almost tripled the risk of MI (RR=2.91; 95% CI 1.07-7.92).
Conclusion - Assessment of vital exhaustion contributes to the identification of subjects at increased risk of MI in general practice.

6.2 Introduction

Prevention of cardiovascular disease (CVD), including myocardial infarction (MI), is an important task for physicians, including general practitioners.[1] Primarily, prevention requires the identification of risk factors. Generally recognized risk factors for MI include older age, male gender, positive family history, smoking habits, hypertension, hypercholesterolemia and diabetes mellitus (DM).

Many patients feel exhausted after an MI.[2,3] Epidemiological studies investigating the precursors of MI have shown that these feelings had already existed before the occurrence of MI in the majority of patients.[4] *Appels* labeled this state as Vital Exhaustion (VE), a state characterized by unusual fatigue, loss of energy, increased irritability and feelings of demoralization.[5] This state reflects a breakdown of the adaptation to stress.

This observation induced us to test whether an assessment of VE could contribute to the identification of subjects at increased risk of MI in general practice. This test was performed in the context of the so-called Mierlo Project.

6.3 Methods

Design

The Mierlo Project was conducted among the adult population of the Dutch village of Mierlo, and the same population was used for this follow-up study. The Mierlo Project consisted of a selection procedure, immediately followed by two intervention studies, one in hypercholesterolemic subjects and one in subjects at risk of CVD. The selection procedure consisted of a simple questionnaire mailed to those inhabitants of the village who were aged between 41 and 66 years.

The questionnaire consisted of six questions regarding the presence or awareness of risk factors for CVD:

Q1. Do you suffer from a cardiovascular disease?
Q2. Does your father or mother or any of your brothers or sisters suffer from a cardiovascular disease or a high cholesterol level?
Q3. Do you suffer from diabetes?
Q4. Do you suffer from hypertension?

Q5. Is your weight in kg. more than your length in cm. minus 100?
Q6. Do you smoke more than five cigarettes a day?

If one or more of the questions on the returned questionnaire had been answered by 'yes' (or undecided), the subject was invited for a further examination at the selection center. The measurements taken at this visit included systolic and diastolic blood pressure (SBP and DBP; recorded twice, at the beginning and at the end of the visit, after which mean values were computed), height and weight (used to calculate body mass index, BMI). In addition, smoking habits (numbers of cigarettes) were asked for, and a venous blood sample was taken for total cholesterol (TC) assay. Blood pressure and cholesterol measurements were performed according to the guidelines of the Dutch College of General Practitioners (NHG).[6,7] The visits took place between May 1993 and May 1995.

At the visit, the subjects underwent the Maastricht Interview on Vital Exhaustion (MIVE).[8] The MIVE was administered by a trained practice nurse and a trained research nurse according to current standards. The interview consists of 23 questions, asking for unusual fatigue, loss of energy, increased irritability and feelings of demoralization, all scored as absent or present. Thus, the minimum score is zero, while the maximum score is 23. The duration of one interview was approximately 15 minutes. Cronbach's alpha for the MIVE was 0.89, indicating a good reliability.

The cohort was followed for about four to five years. In the first year, the cohort followed the regular procedure of the Mierlo Project after the first visit. In subjects with a TC $\geq$ 7.0 mmol/l at the first visit, two additional TC measurements were done within a period of two months. No particular advice about eating habits or lifestyle was given during the visits. Subjects with a mean TC level of 7.0 - 9.9 mmol/l in the three consecutive measurements entered a randomized clinical trial (RCT) (those with TC $\geq$ 10 mmol/l were excluded). The trial medication consisted of the cholesterol-lowering agent magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) or placebo. Subjects with conditions interacting with the medication, such as other lipid-influencing medication, serious heart complaints (during the last three months) and DM were excluded. The follow-up period was one year, and involved three-monthly visits to the GP. More details about the design and results of the RCT have been published elsewhere.[9]

Subjects with a Modifiable Risk Level (MRL) $\geq$8 participated in the

descriptive study. The MRL is calculated by adding the modifiable risk factors TC, DBP, SBP, BMI, exercise and smoking habits, which are assigned a value depending on the severity of the risk (derived and adapted from the method by *Anggard et al.*[10]). Subjects visited their GP every three months over a period of one year. Each visit involved an evaluation of their general condition in terms of CVD: blood pressure and weight were determined and smoking habits and physical activity were discussed. The duration of this study was one year.

Endpoint definition and statistical analysis

The endpoint of the present study was MI, which included the occurrence of nonfatal MI and cardiac death. These were assessed in the period between January 1998 and October 1998, based on data from the GP's patient records. Endpoint diagnoses were confirmed by a medical specialist. An MI was diagnosed if at least two of the three following criteria were fulfilled: characteristic angina complaints during at least 15 minutes; characteristic ECG changes fitting with an MI and increased cardiac enzymes established in the laboratory. Cardiac death was diagnosed if death occurred within one hour after the complaints began. If a person experienced more than one event, the first event was used as the endpoint.

Survival curves with MI as the dependent variable were constructed for the VE and non-VE groups, using the Cox regression model, with both direct and stepwise procedures. Subjects scoring 0-7 were labeled as not vitally exhausted, while those scoring 8-23 were labeled as vitally exhausted, according to the instructions.[8] Covariates included age, gender, SBP, DBP, TC, BMI, smoking habits (yes/no), self-reported CVD (Q1 of questionnaire) and self-reported DM (Q3). Improvement of the model by the addition of VE was tested by the change of the -2log likelihood (forward stepwise). Data were entered into SPSS, version 10.0. All p-values were two-sided.

6.4 Results

The screening questionnaire was sent to 3276 subjects. A total of 3061 questionnaires (93%) were returned. It was found that 455 subjects

(15%) had not answered 'yes' to any of the questions. The remaining 2606 subjects were invited to visit the selection center. This invitation was declined by 146 subjects (6%). Seven subjects (0.2%) did not visit the selection center because they had moved out of Mierlo or had died between the start of the study and the assessments. Of those who visited the selection center, 19 (1%) had to be excluded because of language problems. This left a cohort of 2433 subjects, of whom 167 participated in the RCT and 458 in the descriptive study.

The median duration of follow-up was 50.8 ± 6.5 months, with a range of 2.0 to 62.7 months. During this period, 29 subjects suffered a non-fatal MI; one subject died from MI.

Table 6.1 shows the characteristics of the cohort at their entrance in the study. The table shows that male gender, age, TC and SBP increased the risk of MI at the univariate level. VE just failed to reach the conventional level of statistical significance (RR=2.54; 95% CI 0.97-6.64), due to the confounding effect of gender, with women showing higher exhaustion scores and a smaller risk of MI.

Table 6.1. Baseline characteristics of the cohort; MI versus no MI (%).

	MI		no MI		p
Number of subjects	30		2403		
Age (mean ± SD)	55.9	± 7.0	51.6	± 7.2	0.001
Gender					0.003
male	23	(77)	1186	(49)	
female	7	(23)	1217	(51)	
VE					0.063
yes	5	(17)	173	(7)	
no	25	(83)	2230	(93)	
SBP (mean ± SD)	152	± 22	137	± 19	0.000
TC (mean ± SD)	6.4	± 1.0	5.9	± 1.1	0.016
Suffering from CVD (self report)					0.000
yes	12	(40)	210	(9)	
no	18	(60)	2193	(91)	
Suffering from DM (self report)					0.240
yes	2	(7)	72	(3)	
no	28	(93)	2350	(97)	
Smoking					0.078
yes	15	(50)	804	(33)	
no	15	(50)	1599	(67)	

VE: vital exhaustion; SBP: systolic blood pressure (mmHg); TC: total cholesterol (mmol/l); CVD: cardiovascular disease; DM: diabetes mellitus

Table 6.2. Multivariate analysis of risk factors and MI (n=2433).

	ß	SE	Exp	95%CI	p
VE (yes/no)	1.07	0.51	2.91	1.07 - 7.92	0.036
Age	0.06	0.03	1.07	1.01 - 1.13	0.023
Gender (M/F)	-1.10	0.45	0.33	0.14 - 0.80	0.014
SBP	0..02	0.01	1.02	1.00 - 1.04	0.017
TC	0.26	0.17	1.30	0.93 - 1.83	0.129
Smoking (yes/no)	0.68	0.37	1.97	0.95 - 4.08	0.067
Suffering from CVD (self report)	1.26	0.41	3.51	1.57 - 7.86	0.002
Suffering from DM (self report)	-0.018	0.76	0.98	0.22 - 4.33	0.982

VE: vital exhaustion; SBP: systolic blood pressure (mmHg); both mean of 2 values; TC: total cholesterol; CVD: cardiovascular disease; DM: diabetes mellitus

Controlling for gender, age, SBP, TC, smoking habits, self-reported CVD and DM, the risk of VE was found to be 2.91 (95% CI 1.07-7.92) (table 6.2 and figure 6.1). This confirms the hypothesis. The results of the stepwise procedure showed that a positive self-report of CHD carried the highest risk of MI. The model was significantly improved by the inclusion of SBP and gender. Inclusion of VE in the model led to a further improvement, as indicated by a significant change in the -2log likelihood ratio (table 6.3). No other factors were included in the model.

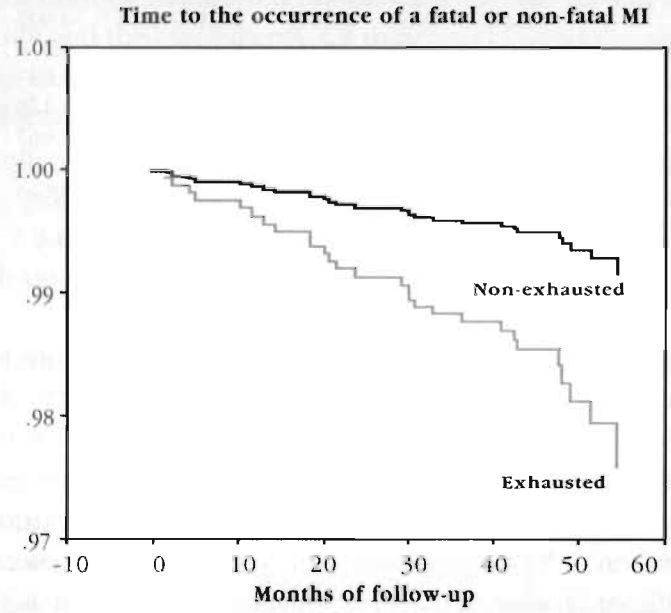
As some subjects were participating in an intervention study, the analyses were repeated, including participation in the RCT and the descriptive study as covariates. Results showed that the risk of VE was not changed by controlling for participation in any of these intervention studies.

Table 6.3. Multivariate analysis of changes in -2log likelihood (forward stepwise) for risk factors and MI (n=2433).

	-2log likelihood	X^2	p
Suffering from CVD (self report)	437.402	40.23	0.000
SBP	426.460	55.02	0.001
Gender (M/F)	421.493	58.70	0.026
VE (yes/no)	417.449	63.19	0.044
Age	412.276	68.38	0.023

CVD: cardiovascular disease; SBP: systolic blood pressure (mmHg); VE: vital exhaustion

Figure 6.1. Kaplan-Meyer estimates of myocardial infarction (MI) in a vitally exhausted (VE) group and a non-VE group. Changes in risk were attributable to the degree of VE. Variables of table 2 were included. P values and changes in risk based on Cox proportional hazards analysis.



6.5 Discussion

The results of a prospective study in a cohort of patients of a group practice showed that an assessment of VE contributed to the identification of patients at increased risk of MI. This result is consistent with earlier studies in which VE was found to be predictive of cardiac events.[2-5] As such, the present study showed that assessment of VE contributed to the identification of subjects at increased risk of suffering an MI within a period of at most five years.

The distinction between VE and depression remains a subject of debate. Depression is also recognized as a predictor of MI.[11] We cannot answer the question whether exhaustion is predictive of MI, because of its overlap with depression. However, a depressed mood, the key symptom of depression, is almost absent in exhausted subjects.[12] Nearly all depressed patients feel exhausted. Of those who are exhausted only 20% meets the

DSM criteria for Major Depression. Cognitive distortions such as 'I do not deserve to be loved' are usually absent in exhausted subjects.

The major limitation of the present study was the validity of the pre-screening questionnaire. Subjects may have endorsed the question (Q1) 'Do you suffer from heart disease?' for different reasons. A negative answer to this question is no valid proof of the absence of CHD. Also no ECG recordings of the subjects were made and, therefore, no ECG evidence of ischemic heart disease is available. The presence of DM, too, was based upon self-report only. Therefore, the present study does not prove that VE is an independent risk factor of MI, because it cannot be ruled out that the feelings of loss of energy and general malaise were caused by existing heart disease in some subjects. However, the prevention of a recurrent cardiac event is as important as the prevention of a first MI. Therefore, the results are meaningful for general practice, despite the fact that the design of the study was not really suitable to test an etiological hypothesis.

The Mierlo study was designed as an intervention study. Controlling for participation in one of the interventions did not change the results. This might be caused by the fact that the RCT did not change TC significantly[9] and that the descriptive study did not influence the risk level to any notable degree. The effects of this descriptive study have not been evaluated. The lack of change might also be caused by the fact that no attempts were made to change the level of exhaustion.

This study among an average Western European village population demonstrates that exhaustion should be taken into account when evaluating an individual's risk of a first or second MI.

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CHAPTER 7

VITAL EXHAUSTION AS A RISK INDICATOR OF FIRST STROKE

Accepted for publication in Psychosomatics. Schuitemaker GE, Dinant GJ, van der Pol GA, Verbelst AFM †, Appels A. Vital exhaustion as a risk indicator of first stroke.

7.1 Abstract

Background – Fatigue is a common condition after stroke. An as yet unresolved question is whether the fatigue is a consequence of the stroke or is one of the precursors.
Objective – To investigate whether vital exhaustion (VE) is a precursor of first stroke, while controlling for other cardiovascular risk factors.
Design – Prospective cohort study
Method – VE was diagnosed using the Maastricht Interview Vital Exhaustion (MIVE). We controlled for age, gender, diabetes mellitus (DM), systolic and diastolic blood pressure (SBP and DBP), total cholesterol (TC), body mass index (BMI) and smoking habits as possible confounders. Data were analysed using Cox regression analysis.
Subjects – Adults (aged 41 – 66) in an average Dutch village population.
Outcome measures – First stroke
Results – VE increased the risk of stroke by 13% per VE point on the MIVE ($p=0.003$). This figure remained statistically significant and hardly changed upon controling for other risk factors. TC, DBP, SBP, DM and smoking also increased the risk of stroke significantly ($p<0.05$).
Conclusion – A state of exhaustion is one of the risk indicators of stroke. This means that the fatigue so often seen after stroke was already experienced by many patients before the occurrence of the stroke.

7.2 Introduction

Worldwide, stroke is the second cause of death after heart disease.[1] Identification of risk factors is the mainstay of primary stroke prevention. In the case of stroke, the factor most generally recognized as the principal risk factor is hypertension.[2] Other risk factors are myocardial infarction (MI), especially in the first month after the event; diabetes mellitus (DM); and smoking. Dyslipidemia, including hypercholesterolemia, has not been clearly established as a risk factor, although some studies with the lipid-lowering 3-hydroxy-3-methylglutaryl coenzyme A reductase agents (statins) have shown a decrease in the risk of stroke after MI.[3,4] One study reported overweight to be associated with increased risk of stroke in middle-aged men,[5] and the level of physical activity may be indirectly connected to stroke risk.[2]

Fatigue is a common condition after stroke. In one study, 68% of 88 men and women diagnosed with stroke reported fatigue problems, against 36% in a control group ($p<0.001$).6 Fatigue was defined as a feeling of physical tiredness and lack of energy.

Similar observations have been made in cardiovascular patients. Many patients feel tired, distressed or even depressed after an MI.[7,8] Epidemiological studies investigating the precursors of MI showed that these feelings had already existed before the occurrence of MI in the majority of patients.[9] This prodromal state was labeled by *Appels* as Vital Exhaustion (VE), a state characterized by unusual fatigue, loss of energy, increased irritability and feelings of demoralization.[10]

This observation induced us to test the hypothesis that a state of exhaustion precedes the onset of stroke and, consequently, is one of the risk indicators of stroke. This hypothesis was tested in the so-called Mierlo Project.

7.3 Methods

Design

The Mierlo Project was conducted among the adult population of the village of Mierlo (the Netherlands). All inhabitants aged between 41

and 66 years received a questionnaire by mail, asking for the presence of cardiovascular risk factors (heredity, DM, hypertension, overweight, smoking habits, cardiovascular condition). Subjects who answered one or more questions in the affirmative were invited to visit a location in the village, separated from the health center and specially equipped for this project. Measurements taken at this visit included systolic and diastolic blood pressure (SBP, DBP), height and weight (used to calculate body mass index, BMI), smoking habits and cholesterol. In subjects with a total cholesterol >7.0 mmol/l, cholesterol assessments were repeated twice. Subjects with a mean total cholesterol level > 7.0 mmol/l for the three assessments were invited to participate in a randomized clinical trial investigating the effect of a lipid lowering drug. Subjects who were found to be at increased risk for CVD according to a model adapted from *Anggard et al.*[11] were invited to visit their GP every three months over a period of one year for surveillance and counseling with regard to their cardiovascular risk profile (monitoring study). Details about both interventions have been described elsewhere.[12]

At the first visit to the health center all subjects underwent the Maastricht Interview Vital Exhaustion (MIVE; appendix).[13] The MIVE was administered by a trained practice nurse and a trained research nurse according to current standards. The interview consists of 23 questions, asking for unusual fatigue, loss of energy, increased irritability and feelings of demoralization, all scored as absent or present. Thus, the minimum score is zero, while the maximum score is 23. The duration of one interview was approximately 15 minutes. Those who were interviewed constituted the cohort of the study presented below.

Endpoint definition and statistical analyses

The endpoint assessed in the present study was first stroke. If a person was found to have suffered more than one stroke since the original examination, the first event was regarded as the endpoint. The endpoint was assessed in the period between January 1998 and October 1998, based on data from the GP's patient records. The International Classification of Primary Care (ICPC) was used to define stroke. Endpoint diagnoses were confirmed by a medical specialist.

Patient records were inspected to exclude the possibility that VE could have been caused by a previous stroke. One subject was found to have suffered a stroke before the interview and was excluded. None of those who suffered a stroke during the follow-up period had suffered any strokes before enrollment in the study.

Data were analysed by means of the Cox regression analyses, using continuous VE scores. Since the number of incident cases of stroke was small, which might result in unstable risk estimates, data were analyzed in two steps. The first step involved calculating the risk of exhaustion using Cox regression analysis and controlling for one possible confounder. In the second step, all factors found to be associated with incident stroke in the first step were simultaneously included in a Cox regression analysis. If the risks computed in the second analysis are comparable to that computed in the first step, one may assume that the estimates of the multivariate model are not seriously invalidated by the small number of incident cases. We also used a dichotomous score 'exhausted – not exhausted', using a cut-off point between the ranges 0-7 and 8-23.[13]

The independent covariates included were age, gender, TC, SBP, DBP, DM (question no. 3 of the questionnaire), body mass index (BMI) and smoking habits (yes/no). Data were entered into SPSS, version 8.0. All P-values were two-sided.

7.4 Results

The screening questionnaire was sent to 3276 subjects. A total of 3061 questionnaires (93%) were returned. It was found that 455 subjects (15%) had not answered 'yes' to any of the questions. The remaining 2606 subjects were invited to visit the selection center. This invitation was declined by 147 subjects (6%). Seven subjects (0.2%) did not visit the selection center because they had moved out of Mierlo or had died between the start of the study and the assessments. Of those who visited the selection center, 19 (1%) had to be excluded because of linguistic problems. This left a cohort of 2432 subjects, of whom 167 participated in the RCT and 458 in the monitoring study.

The median duration of follow-up was 50.9 ± 6.1 months, with a range of 9.5 to 62.7 months. During this period, 14 subjects suffered a first

stroke; seven men and seven women.

Table 7.1 shows the characteristics of the cohort at the time of examination and the administration of the MIVE, as well as univariate analyses using t-tests and X^2-tests.

Table 7.1. Baseline characteristics of cohort; stroke versus no stroke.

	Stroke	no stroke	p
Number subjects	14	2418	
Gender (M/F)	7/7	1202/1216	1.000
Age (mean ± SD)	54.2 ± 6.4	51.3 ± 7.3	0.130
VE (mean ± SD)	6.7 ± 6.7	3.1 ± 4.3	0.002
TC (mean ± SD)	6.8 ± 1.0	5.9 ± 1.1	0.004
DBP (mean ± SD)	90 6 ± 15.3	84.4 ± 10.9	0.036
SBP (mean ± SD)	151.4 ± 27.4	137.4 ± 19.3	0.007
BMI (mean ± SD)	25.9 ± 4.1	26.4 ± 3.8	0.680
DM(self report) (yes/no)	4/10	69/2349	0.001
Smoking (yes/no)	11/3	808/1610	0.001

VE: vital exhaustion; TC: total cholesterol (mmol/l); DBP: diastolic blood pressure (mmHg); SBP: systolic blood pressure (mmHg); BMI: body mass index (kg/m^2); DM: diabetes mellitus

Risk of stroke increased by 13% for each additional VE point on the MIVE (table 7.2). This figure was statistically significant and hardly changed upon controlling for other possible confounders. When all possible confounders were included simultaneously in the equation, the relative risk associated with VE remained unchanged (RR=1.13).

The relative risk associated with exhaustion using a dichotomous score and controlling for all possible confounders simultaneously was estimated as 3.52 (95%CI 0.97-12.73).

Since the Mierlo Project included two intervention studies, we checked whether participation in one of these two studies influenced the association between VE and stroke. None of the future stroke patients had participated in the RCT. Furthermore, the results of the RCT indicated that the lipid-lowering agent had no significant effect compared to placebo.[13] Five of the future stroke victims had participated in the monitoring study. Controlling for participation in that study did not influence the results of the Cox regression analysis.

Highly significant associations were also found for DM (Exp. 12.20;

Table 7.2. VE as a risk predictor of stroke, using a Cox regression analysis and controlling for various single factors.

	n	ß	SE	Exp	95%CI	p
VE	2432	0.12	0.04	1.13	1.04 - 1.23	0.003
VE	2432	0.12	0.04	1.13	1.04 - 1.23	0.003
Age		0.07	0.04	1.07	0.99 - 1.15	0.071
VE	2432	0.13	0.04	1.13	1.04 - 1.23	0.003
Gender		-0.22	0.54	0.80	0.28 - 2.32	0.682
VE	2425	0.13	0.04	1.13	1.04 - 1.23	0.003
TC		0.66	0.22	1.93	1.25 - 2.98	0.003
VE	2432	0.13	0.04	1.14	1.05 - 1.23	0.002
DBP		0.05	0.02	1.05	1.00 - 1.09	0.029
VE	2432	0.13	0.04	1.14	1.05 - 1.24	0.002
SBP		0.03	0.01	1.03	1.02 - 1.06	0.003
VE	2427	0.12	0.04	1.13	1.04 - 1.23	0.003
BMI		-0.02	0.07	0.98	0.85 - 1.12	0.748
VE	2432	0.11	0.04	1.12	1.03 - 1.21	0.007
DM (self report)		2.50	0.60	12.20	3.78 - 39.45	0.000
VE	2432	0.12	0.04	1.12	1.03 - 1.21	0.008
Smoking (yes/no)		1.87	0.65	6.48	1.80 - 23.29	0.004

VE: vital exhaustion; b: regression coefficient; SE: standard error; Exp: exponent; TC: total cholesterol (mmol/l; DBP: diastolic blood pressure (mmHg); SBP: systolic blood pressure (mmHg); BMI: body mass index (kg/m^2); DM: diabetes mellitus

p=0.000), smoking (6.48; 0.004), TC (1.93; 0.003), DBP (1.05; 0.029) and SBP (1.03; 0.003) (table 7.2). This implies that an individual with an SBP of 160 mmHg has a 3 x 65 = 190% increased risk, compared to an individual with an SBP of 95 mmHg.

7.5 Discussion

This study tested the hypothesis that feelings of tiredness and distress are among the precursors of stroke. As hypothesized, feelings of VE increased the risk of stroke. The increased risk associated with this state could not be attributed to VE being a side-effect of other risk factors.

The major limitation of this study was the small number of incident cases. This reduced the precision of the estimates of the risk associated with all risk factors, as reflected in the rather large confidence intervals. Because of the small number and the loss of information when the VE values were collapsed into an exhausted and a non-exhausted group, the

relative risk associated with VE as a dichotomous variable just failed to reach the conventional level of statistical significance (95%CI 0.97-12.73). The small number of cases also prevented us from examining whether the association between VE and stroke differed between time intervals. We cannot rule out the possibility that some symptoms are markers of subclinical cerebrovascular disease. A second limitation was formed by the fact that the diagnosis of diabetes mellitus was based on self-reports. This may have resulted in an imprecize estimation of DM.

The data of the Mierlo project fit in well with recent observations showing that depression is predictive of stroke.[14,15] We cannot answer the question whether exhaustion is predictive of stroke, because of its overlap with depression. The present study did not measure depression, and no data about anti-depressive medication were available. An item analysis of the MIVE indicated that the following items (in descending order of strength of the association) were significantly associated with stroke: lack of energy, giving up trying, inability to accomplish, feeling dejected, decreased energy, crying (or an inclination to cry), feelings of irritability and hopelessness.

We have used the word risk indicator instead of risk factor, because pathophysiological aspects of the relation between stroke and vital exhaustion can only be speculated about. An indirect clue may be insulin resistance, as a condition which may be related to both vital exhaustion[16] and stroke.[17,18] A pattern of pituitary and adrenocortical responses, associated with insulin resistance syndrome, might be an underlying pathophysiological mechanism.

The present study may present an incitement for further studies, to find out whether VE may be a predictor or even a risk factor for stroke and to try and clarify the pathophysiological nature of this association, focusing on hormonal factors, especially with regard to insulin metabolism.

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CHAPTER 8

A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL OF MAGNESIUM-PYRIDOXAL-5'-PHOSPHATE-GLUTAMATE FOR HYPERCHOLESTEROLEMIA AND OTHER CLINICAL-CHEMICAL RISK FACTORS OF CARDIOVASCULAR DISEASE IN A PRIMARY CARE SETTING

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8.1 Abstract

Background - Lipid-lowering drugs are extensively used in primary care to reduce the risk of cardiovascular disease (CVD). Apart from high total cholesterol (TC), several other clinical-chemical variables are associated with the risk of CVD. Magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) has been found to have a positive influence on TC levels and other clinical-chemical values in some selected populations.
Objective - To assess, in a general practice setting, the efficacy and clinical effectiveness of MPPG in the treatment of clinical-chemical risk factors for CVD.
Design - Randomized double-blind, placebo-controlled, clinical trial, lasting 12 months.
Patients - Adults (25-66 years) in an average Dutch village population with serum cholesterol levels between 7.0 mmol/l and 9.9 mmol/l.
Intervention - Subjects were assigned at random to treatment with MPPG (3 x 150 mg daily) or placebo. Clinical-chemical parameters were assessed at 1, 3, 6, 9 and 12 months (t_1, t_2, t_3, t_3, t_4). Efficacy was measured at t_2. Long-term effect (clinical effectiveness) was measured by combining the results at t_2, t_3, t_4 and t_5 (t_{2-5}).
Outcome measures - TC (primary), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides, apolipoprotein-A1 (Apo-A1), apolipoprotein-B100 (Apo-B), fibrinogen (FB) and lipoprotein a [Lp(a), secondary].
Results - No statistically significant differences in the efficacy and effectiveness of TC were found between the MPPG group and the placebo group. The same was demonstrated for the other clinical-chemical values, except for LDL-C (effectiveness, p=0.04).
Conclusions - Efficacy and effectiveness of MPPG are too poor to be of relevance for application as a lipid-lowering drug in GP.

8.2 Introduction

Hypercholesterolemia has been established as one of the major risk factors for cardiovascular disease.[1,2] The risk of myocardial infarction in middle-aged, apparently healthy men can be reduced by lowering cholesterol levels.[3-5]

The Dutch guidelines, issued in 1998, recommend as medication of first choice the hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins).[6] This choice is mainly based on their potent action on total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) levels. Although the effects of the individual statins differ, they generally also exert an effect on apolipoprotein-B100 (Apo-B), and to a lesser extent on high density lipoprotein-cholesterol (HDL-C), apolipoprotein-A1 (Apo-A1) and triglycerides.[5,7-12] As such, the statins are more potent than the older type cholesterol-lowering drugs such as niacin, the bile acid sequestrants and the fibrates.

Although they are considered safe drugs for prevention, all of these have their side effects. The statins must not be prescribed in cases of liver and kidney dysfunction, during pregnancy and lactation or to women with insecure contraception. Most side effects are gastro-intestinal.[5,7-12]

In the same period in which the statins were being developed, studies using scientific standards were performed with magnesium-pyridoxal-5'-phosphate-glutamate (MPPG), a vitamin B6 derivative.[13-15] Several studies of MPPG were conducted in vitro, as well as in animals and humans. In vitro experiments showed an antioxidative effect of MPPG on LDL-C[16,17] and an anticoagulant/antiplatelet effect.[18] Calcium-antagonistic effects of MPPG were found in polymyopathic Syrian hamsters[19] and antiatherosclerotic effects in rabbits and rats[20,21] These effects were accompanied by a cholesterol-lowering effect. The mechanism of this effect remains unclear. It cannot be explained on basis of action of the single constituents magnesium, vitamin B6 or glutamate. None of these shows a cholesterol lowering effect.

Most human studies with MPPG have been unblinded, uncontrolled, non-randomized or unpublished. Nevertheless, the outcome tendency has been that MPPG has a favourable effect on TC, LDL-C, HDL-C and triglycerides. Three carefully designed, double-blind, placebo-controlled, randomized clinical trials have been published.[13-15] The first was done in

patients with renal insufficiency (MPPG/placebo: 15/15), treated with three times daily doses (dd) 50 mg MPPG daily for 12 weeks[13], the second in patients with type IIb hyperlipidemia (74/75), treated with daily 3 dd 150 mg for 6 months[14] and the third in patients with familial hypercholesterolemia (9/10), treated with either 3 dd 150 mg daily for 8 weeks or 4 dd 150 mg for eight consecutive weeks[15]. The first two studies demonstrated a considerably favourable effect of MPPG, compared with placebo, on TC, LDL-C, HDL-C and triglycerides. These results could not be confirmed by the third study. So far, no effects have been demonstrated on Apo-A1 and Apo-B[14,15], fibrinogen (FB)[13] or lipoprotein (a) [Lp(a)][15]. The authors of this last study[15] could not give an adequate explanation for their divergent results.

On the basis of the pharmacological properties of MPPG, the likely effects of this substance on primary hypercholesterolemia and mixed dyslipidemia, the low-risk profile with hardly any adverse effects and the fact that a cholesterol-lowering drug is primarily a tool in the hands of general practitioners (GPs), we found it worthwhile to investigate the efficacy and effectiveness of MPPG compared with placebo in a GP-setting. Efficacy was calculated by comparing differences in mean cholesterol levels after an intervention period of 3 months, whereas a period of 12 months was used to study the clinical effectiveness of MPPG.

8.3 Methods

Setting and ethical approval

The study was conducted between May 1993 and December 1996 in Mierlo, a village with approximately 10,000 inhabitants, 15 km southeast of Eindhoven (in the southern part of the Netherlands). Prior to the randomized, placebo-controlled, double-blind intervention trial (RCT), the entire adult population of this village entered a selection protocol aimed at detecting subjects with an increased risk of cardiovascular disease. Enrolment in the RCT took place simultaneously with the selection part of the study.

In Mierlo, five GPs collaborate in one health center, which also houses the local pharmacy. The selection procedure was conducted at

one location in the village, separated from the health center and specially equipped for this purpose. At this selection center, one experienced practice-research nurse and one previously trained research nurse were responsible for the logistics (mailings, making appointments, transportation of blood samples) and the physical examinations (blood pressure, height, weight). They also asked the patients about their physical activities and smoking habits and conducted the blood sampling (also during the RCT). Their training was based on the relevant Practice Guidelines of the Dutch College of General Practitioners (NHG).[22,23]

All five GPs participated in the RCT. Each GP was responsible for those patients who were on his list. One GP was also responsible for a group of patients who were on the list of a GP outside the village or who had no GP at all. The pharmacy's task was the storage and supply of the trial medication.

The samples were analyzed at the laboratory of the local hospital in Geldrop. This laboratory is involved in a national quality assurance program.

The protocol for the RCT was approved by the medical ethics committee of Maastricht University and the University Hospital Maastricht (the Netherlands).

Subjects, randomization and power

On the basis of the municipal register, all inhabitants of the village born between 1 January 1928 and 31 December 1968, and thus aged 26 years to 66 years at the time of the RCT, were recorded in the database. These subjects were sent a questionnaire by mail.

The questionnaire consisted of six questions regarding the presence or awareness of risk factors for cardiovascular diseases:

1. Do you suffer from a cardiovascular disease?
2. Does your father or mother or any of your brothers or sisters suffer from a cardiovascular disease or a high cholesterol level?
3. Do you suffer from diabetes?
4. Do you suffer from hypertension?
5. Is your weight in kg. more than your length in cm. minus 100?
6. Do you smoke more than five cigarettes a day?

If one or more of the questions on the returned questionnaire had been answered by 'yes' (or undecided), the subject was invited for a further examination at the selection center. The examination involved diastolic and systolic blood pressure measurements, in accordance with the NHG Practice Guideline on Hypertension[22], at the beginning and at the end of the visit. In between these measurements, their height and weight were measured and standardized questions were asked about physical activity (much, little or no exercise according to the subject's own opinion) and smoking habits (number of cigarettes per day). A venous blood sample was taken for TC assay. Since the screening procedure involved the total adult population, the subjects' medication was not taken into account.

Subjects with TC of at least 7.0 mmol/l were invited for a second and a third visit. At the second visit, the above procedure was repeated, except for the height measurement. The third visit was similar to the second. This time, subjects were asked in advance to fast (i.e. no food or drink, except water, tea or coffee without cream or sugar, from 2200 hours the previous evening), since levels of HDL-C, triglycerides, Apo-A1, Apo-B, Lp(a) and FB were to be assayed. LDL-C values were calculated using the Friedewald formula. If the triglyceride value was above 4.0 mmol/l, no calculation for LDL-C was made.

TC was measured in accordance with the NHG Practice Guideline on Cholesterol.[23] Three measurements were made within a 2-week time span. If the mean TC was at least 10.0 mmol/l, the person was advized to consult his GP and was excluded from further selection. No particular advice about eating habits or lifestyle was given during the visits.

Subjects with a mean TC level of between 7.0 mmol/l and 9.9 mmol/l (mean of three measurements) were invited to enter the trial. At the subjects' first visit with the GP (ç) it was decided whether they were suitable for the intervention trial. Exclusion criteria for the trial were the use of lipid-influencing medication (thiazide diuretics, beta-blockers, calcium antagonists, corticosteroids or other lipid-lowering agents during the last 4 weeks), drastic dietary changes (during the last month), use of megadosages of vitamins/minerals (during the last 2 months), recent excessive loss of fluid, alcohol use (more than 5 units per day), regular drug use, participation in another trial (during the last 3 months), pregnancy, lactation, insecure contraception, serious heart complaints (during the last 3 months), diabetes mellitus, pancreatitis (acute or

chronic), hypo/hyperthyroidism, obstructive bile duct disorders, acute porphyria, anorexia nervosa, gout (uric acid >7 mg/dl), glycogen storage disease, pituitary/adrenal disorders or primary liver diseases.

After inclusion, written informed consent was obtained from the subjects. No wash-out period was used since it was impracticable in the whole screening procedure. The trial medication, MPPG or placebo, was assigned according to a stratified randomization scheme. Stratification was applied for TC (7.0-7.9 mmol/l and 8.0-9.9 mmol/l), gender and age (26-45 years and 46-66 years). This resulted in eight groups, which were then randomized in blocks of ten.

On the basis of power calculations (assuming a 20% reduction of mean TC by MPPG compared with placebo, with a two-sided significance level of 0.05 and a power of 90%), a total of 200 subjects were needed to obtain significant results. Initially, the lower limit was set at 7.5 mmol/l. However, it soon became clear that this limit had to be reduced to 7.0 mmol/l, to obtain enough subjects.

Intervention, blinding and assignment

The trial medication was a coated tablet containing 150 mg MPPG or placebo. The dosage was three tablets per day. One package contained 100 tablets. Each subject received three packages (i.e. 300 tablets) every 3 months (starting at t_0). Each subject received his medication at the pharmacy on prescription from the GP. In those cases where the GP deemed it necessary to break the blinding, e.g. when a serious intercurrent disease developed, he asked the practice-research nurse to give him the required information. He then excluded the patient from further follow-up.

Follow-up

At t_0, the practice-research nurse scheduled appointments with the subjects for blood sampling (at the selection center) and for the consultations with the GP during the follow-up period, i.e., at 1, 3, 6, 9 and 12 months (t_1, t_2, t_3, t_4 and t_5, respectively). The procedure for the follow-up visits to the GP was identical to that at the second and third selection

visits (except for the blood sampling). Subjects were also asked about pregnancy, change of contraception, drastic dietary changes, use of megadosages of vitamins/minerals and other medication, excessive loss of fluids, serious heart complaints or other complaints. At every consultation the GP discussed dietary habits and lifestyle with regard to risk factors for cardiovascular diseases (unstandardized) and, if necessary, recommended any improvements he felt were called for.

Once every 3 months, i.e., at t_2, t_3, t_4 and t_5, treatment compliance was checked by the GP using pill counts. A percentage of 80-120, as calculated on the basis of three tablets a day, was considered a good medication compliance.

Subjects could ask to be informed of their personal outcomes, including their TC, at any time during the study; the relevant information was supplied either by the research nurse or by their own GP.

No specific stopping rules were formulated. Termination occurred by the subject's own decision or if the GP estimated this to be in the interest of the subject's health. Drop-outs during the intervention were interviewed, as far as possible, to find out the reason why they had quit.

Laboratory methods

Blood sampling was done with a vacuum tube system (Becton Dickinson). For all parameters, except for FB, tubes with a gel were used. Assays were done in serum. Citrated blood (1:10) was used for FB and the assay was done on plasma.

At the time of blood sampling, the participants were fasting, except when TC only was sampled. The samples were kept at room temperature and transported for analysis to the nearby hospital laboratory at the end of every day for analysis. Thereafter, the samples were either processed immediately or were stored at -30°C.

Assays were done for TC with the cholesterol oxidase/p-amino-phenazone (CHOD-PAP) method, using the Boehringer method on a Hitachi 911; for TG with an enzymatic method (no correction for glycerol, using the Boehringer method on a Hitachi 911); for HDL-C with the IL CHOD-PAP method on an IL Monarch analyzer, after precipitation with polyethylene glycol/dextranesulphate/Mg; for Apo-A1 and Apo-B using the Beckman

Array (Beckman reagents); for FB with thrombin according to the Clauss method on the Boehringer STA compact analyser; and for Lp(a) on the Beckman Array with immuno-antiserum and standard Beckman buffer. LDL-C was calculated with the help of the Friedewald formula. The TC and FB assays have been standardized with other laboratories.

Laboratory reference values are: TC (4.0-6.5 mmol/l), LDL-C (3.9-4.9 mmol/l), HDL-C (male: 0.90-1.40 mmol/l; female: 1.20-1.60 mmol/l), triglycerides (0.8-2.0 mmol/l), Apo-A1 (male: 0.94-1.78 g/l; female: 1.01-1.98 g/l), Apo-B (male: 0.63-1.33 g/l; female: 0.60-1.26 g/l) and FB (2.0-4.0 g/l). No reference value was available for Lp(a) due to the nature of this variable.

The laboratory participated in the Dutch foundation for quality control in clinical hospital laboratories (SKZL).

Statistical analysis

Data were entered into SPSS, version 8.0. The analysis was based on intention-to-treat principles. Missing values were substituted with the mean value of the placebo at the corresponding time point, including t_0. Thus, no subjects were removed from the data analysis. Analysis was divided into two parts. The efficacy of MPPG was calculated by comparing the mean values at t_2 in the MPPG group with those in the placebo group, using TC as the primary effect parameter. Secondary effect parameters were LDL-C, HDL-C, triglycerides, Apo-A1, Apo-B, FB and logLp(a), because of skewed distribution. The effectiveness of MPPG was analyzed over a period of 12 months. For this purpose, the mean values at t_2, t_3, t_4 and t_5 were combined (t_{2-5}) in the MPPG and the placebo groups. Linear regression analysis was used to check for significant differences in mean values of both efficacy and effectiveness between MPPG and placebo at t_0.

8.4 Results

Subject inclusion and baseline characteristics

Subject disposition during the selection is summarized in table 8.1.

Four thousand and ninety subjects underwent the first examination in the selection center. Five hundred and six subjects with TC of at least 7.0 mmol/l participated in the second examination and 492 in the third.

From these three measurements the mean serum cholesterol (TC-mean) was calculated, which served as the initial TC-value at t_0. The mean values of the three consecutive measurements and the mean value of TC-mean were 7.58, 7.25, 7.27 and 7.35 mmol/l, respectively, so the phenomenon of regression to the mean was evident. Three hundred and seventy-seven subjects had a TC-mean between 7.0 mmol/l and 9.9 mmol/l and were selected to enter the RCT.

Table 8.1. Results of the selection process (%).

Registered	5894	(100)
Unreturned questionnaires	526	(9)
Returned questionnaires	5368	(91)
All questions 'no'	973	(17)
At least one question 'yes' or undecided	4395	(75)
Refused	292	(5)
Moved/died	13	(0)
Screened 1x	4090	(69)
TC<7.0	3575	(61)
No TC measurement available	9	(0)
Screened 2x	506	(9)
Did not show up	15	(0)
Screened 3x	492	(8)
TC-mean<7.0	112	(2)
TC-mean≥ 10.0	2	(0)
Eligible (7.0≤TC-mean<10.0)	377	(6)
Excluded	116	(2)
Refused participation	54	(1)
Other reasons	5	(0)
Randomized	202	(3)

TC: total cholesterol (mmol/l); TC-mean: mean value of three measurements.

Of these 377 subjects, 116 were excluded for various reasons: 73 used lipid-influencing medication (including 19 lipid-lowering agents), 48 suffered from diseases (including 9 with serious heart complaints, 12 with diabetes and 2 with both) and 28 were excluded for other reasons. Furthermore, 54 subjects refused participation, 3 subjects moved and 2 were advized by their GP not to participate. In the end, 202 subjects entered the RCT.

Table 8.2 shows the baseline characteristics for the MPPG and placebo groups. Compared with men, a relatively large number of women over 50 years of age were assigned to both groups. No statistically significant

differences for TC-mean, age and gender were found between the two groups. Except for Apo-A1 (p=0.01), there were no significant differences between the two groups for the other clinical-chemical values at baseline. However, values of TC-mean, triglycerides, Apo-B, body mass index (BMI), little or no exercise and prominent smoking tended towards a more elevated risk in the placebo group than the MPPG group. The distributions in both groups were normal, except for Lp(a). In the course of the intervention period there were no significant changes in either of the groups with regard to blood pressure, BMI, exercise or smoking habits.

Table 8.2. Baseline characteristics of subjects. Numbers are given.

		MPPG (%)	placebo (%)
Total		98 (100)	104 (100)
Male (26-50 y)		46 (47)	40 (39)
Male (51-66 y)		8 (8)	21 (20)
Female (26-50 y)		15 (15)	21 (20)
Female (51-66 y)		29 (30)	22 (21)
Age	mean ± SD		
	median modus	48.8 ± 9.6	48.9 ± 9.1
BP (mmHg)[2]	mean ± SD	134 ± 19 / 83 ± 9	133 ± 17 / 82 ± 10
BMI (kg/m²)[4]	mean ± SD	26.7 ± 3.4	26.8 ± 3.3
Exercise[3]	much	10 (10)	2 (2)
	little or no	88 (90)	102 (98)
No. of cigarettes[3]	0-5	60 (61)	54 (52)
	>5	38 (39)	60 (48)
TC-mean (mmol/l)[1]	mean ± SD	7.6 ± 0.5	7.6 ± 0.5
LDL-C (mmol/l)	mean ± SD	5.2 ± 0.6	5.1 ± 0.6
HDL-C (mmol/l)	mean ± SD	1.43 ± 0.41	1.37 ± 0.46
Triglycerides (mmol/l)	mean ± SD	2.2 ± 1.4	2.3 ± 1.4
Apo-B (g/l)	mean ± SD	1.93 ± 0.26	1.97 ± 0.29
Apo-A1 (g/l)	mean ± SD	1.44 ± 0.24	1.36 ± 0.02
Lp(a) (mg/l)	median (min/max)	214 (10/1818)	190 (16/1980)
	> 300 (mg/l)	37	37
FB (g/l)	mean ± SD	3.2 ± 0.6	3.1 ± 0.6

[1] mean of 3 values (measured at 3 consecutive times);
[2] BP: blood pressure; mean of 6 values (measured twice at 3 consecutive times);
[4] measured at t_0. BMI: body mass index; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo-B: apolipoprotein-B100; Apo-A1: apolipoprotein-A1; Lp(a): lipoprotein (a); FB: fibrinogen; Cholesterol from mmol/l to mg/dl: multiply by 38.67; Triglycerides from mmol/l to mg/dl: multiply by 88.57

Table 8.3. Mean levels and mean percentage changes, compared to baseline values, MPPG versus placebo, at t_2 and at t_{2-5}, compared to t_0.

	baseline	t2		t2-5	
	mean (SEM)	mean (SEM)	% change mean (SEM)	mean (SEM)	% change mean (SEM)
TC (mmol/l)					
MPPG (98)	7.58 (0.05)[1]	7.39 (0.07)	- 0.02 (0.01)	7.38 (0.04)	- 0.02 (0.01)
Placebo (104)	7.59 (0.05)[1]	7.40 (0.06)	- 0.02 (0.01)	7.40 (0.05)	- 0.02 (0.01)
LDL-C (mmol/l)					
MPPG (98)	5.20 (0.06)	4.97 (0.06)	- 0.04 (0.01)	4.98 (0.05)	- 0.04 (0.01)
Placebo (104)	5.14 (0.06)	5.07 (0.07)	- 0.01 (0.01)	5.06 (0.05)	- 0.01 (0.01)
HDL-C (mmol/l)					
MPPG (98)	1.43 (0.04)	1.44 (0.04)	0.02 (0.01)	1.41 (0.03)	0.01 (0.02)
Placebo (104)	1.37 (0.05)	1.38 (0.04)	0.02 (0.01)	1.37 (0.04)	0.03 (0.02)
Triglycerides (mmol/l)					
MPPG (98)	2.24 (0.14)	2.32 (0.14)	0.17 (0.06)	2.37 (0.11)	0.23 (0.06)
Placebo (104)	2.34 (0.14)	2.19 (0.10)	0.05 (0.04)	2.24 (0.08)	0.09 (0.04)
Apo-B (g/l)					
MPPG (98)	1.93 (0.03)	1.87 (0.03)	- 0.03 (0.01)	1.86 (0.02)	- 0.03 (0.01)
Placebo (104)	1.97 (0.03)	1.92 (0.03)	- 0.01 (0.01)	1.91 (0.02)	- 0.02 (0.01)
Apo-A1 (g/l)					
MPPG (98)	1.44 (0.02)	1.47 (0.03)	0.03 (0.01)	1.47 (0.02)	0.04 (0.01)
Placebo (104)	1.36 (0.02)	1.41 (0.02)	0.04 (0.01)	1.45 (0.02)	0.07 (0.01)
Lp(a) (mg/l)					
MPPG (98)	360 (40)	363 (38)	0.59 (0.24)	349 (30)	0.72 (0.24)
Placebo (104)	340 (36)	368 (38)	0.46 (0.20)	377 (40)	1.15 (0.31)
FB (g/l)					
MPPG (98)	3.16 (0.06)	3.27 (0.06)	0.05 (0.02)	3.34 (0.04)	0.07 (0.01)
Placebo (104)	3.14 (0.06)	3.34 (0.07)	0.08 (0.02)	3.35 (0.05)	0.09 (0.01)

[1] mean of 3 values (measured at 3 consecutive times); TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo-B: apolipoprotein-B100; Apo-A1: apolipoprotein-A1; Lp(a): lipoprotein (a); FB: fibrinogen; Cholesterol from mmol/l to mg/dl: multiply by 38.67; Triglycerides from mmol/l to mg/dl: multiply by 88.57

Efficacy and effectiveness

Neither at t_2 (efficacy) nor at the mean of t_{2-5} (clinical effectiveness) were statistically significant changes in TC values found between the MPPG group and the placebo group in the total population. The same was demonstrated for the other clinical-chemical values, except for LDL-C, which was found to be decreased to a clinically relevant extent (p=0.04) despite the relatively small absolute changes. Differences at t_0 between the

Table 8.4. Statistically significant values for efficacy (t2) and effectiveness (t2-5) of MPPG versus placebo in the total population and in some subpopulations ($p<0.05$).

		n	LDL-C	Apo-B	Apo-A1
		MPPG/ placebo			
t_2	BMI ≤ 25.0 (kg/m²)	33/33	0.01	0.01	
	No. of cigarettes (>5/day)	38/60	0.03		
t_{2-5}	Total	98/104	0.04		
	Female	44/43			0.02
	BMI ≤ 25.0 (kg/m²)	33/33		0.04	
	Exercise (little or no)	88/102	0.03		
	BP diastolic <95 mmHg	67/88	0.02		

LDL-C: low density lipoprotein cholesterol; Apo-B: apolipoprotein-B100; Apo-A1: apolipoprotein-A1; BMI: body mass index; BP: blood pressure.

MPPG group and the placebo group could not account for these results.

Table 8.3 shows in more detail the means of the clinical-chemical values, with the mean percentage changes between MPPG and placebo at t_2 and t_{2-5}, compared with t_0. Values of TC, LDL-C and Apo-B showed a slight decrease in both groups, while HDL-C remained about the same and Apo-A1, lp(a) (except for t_{2-5} in the MPPG group) and also FB showed a rise. The exception was formed by the triglycerides; the MPPG group showed a rise, whereas the placebo group showed a decrease (both at t_2 and t_{2-5}).

Regarding efficacy and effectiveness, statistical tests were also executed for the following subgroups: male/female; age (<50 years, ≥50 years); BMI (≤25.0 kg/m², >25.0 kg/m²); smoking (≤5 cigarettes/day, >5 cigarettes/day); diastolic blood pressure (<95 mmHg, ≥95 mmHg); systolic blood pressure (≤160 mmHg, >160 mmHg) and exercise (no or little, much). Significant results ($p<0.05$) are shown in table 8.4. A significant difference for triglycerides, with a higher value in the MPPG group than in the placebo group, was found in the subpopulation diastolic blood pressure less than 95 mmHg (t_{2-5}).

Safety analysis and compliance

Total drop-out was 35% (70 of 202), most of them between t_0 and

Table 8.5. Drop-outs during follow-up.

	MPPG	placebo
Dropped out (after baseline)	36	34
CVD complaints	2	2
GI complaints	5	6
Pruritus, exanthema	0	2
Other diseases	5	4
No change cholesterol	1	1
Drop-out announced	2	1
Drop-outnot announced	21	18

CVD: cardiovascular disease; GI: gastro intestinal; MPPG: magnesium-pyridoxal-5'-phosphate-glutamate

t_2 (18 in the MPPG group and 13 in the placebo group). During the intervention period, the pattern of withdrawal was comparable in both groups (MPPG and placebo, see table 8.5). It is unlikely that complaints were related to the treatment.

Twenty-one subjects in the MPPG group and 18 in the placebo group left the study by simply not showing up at the scheduled visit to the GP or the scheduled blood sampling, despite attempts to convince them to continue their participation. Medication compliance, as defined through pill count, varied in both groups from 67% to 79% of those still participating at the times of the various measurements, with no significant differences between the MPPG and placebo populations.

8.5 Discussion

This study was conducted in a primary care setting in order to establish the cholesterol-lowering effect of MPPG in the hands of a GP over a longer period. Except for an effect on LDL-C, no systematic pattern was seen in the effect of MPPG on the clinical-chemical values. Although the efficacy of MPPG did show a statistically significant difference with placebo for LDL-C in the total population and in some subpopulations (see table 8.4), the clinical relevance of MPPG remained poor because no effectiveness could be detected on TC. Furthermore, compared with placebo, the lowering effect of MPPG on LDL-C was small (table 8.3). Finally, MPPG showed an elevating effect on triglycerides, whereas placebo caused a lowering effect (not significant). In the subpopulation with low diastolic blood pressure, this value was even highly significant ($p=0.01$).

The difference between MPPG and placebo showed a fairly high

level of significance in subjects with BMI of no more than 25 kg/m² as regards LDL-C and the related apolipoprotein Apo-B (both p=0.01). No explanation was found for this phenomenon.

Two other placebo-controlled studies, both with divergent designs, have shown significant effects of MPPG.[13,14] There is no explanation for the discrepancy with the results in our study. The relatively poor results in our study correspond with those in a study of patients with familial hypercholesterolemia.[15] In that study, the dosage of MPPG used was relatively high, but the number of participating subjects was small. The authors suggested that their disappointing results might have been a consequence of the short duration of their study or the type of dyslipidemia in the subjects selected. Since our intervention lasted for 1 year and was performed in an average hypercholesterolemic, relatively large population, we consider it unlikely that selection bias has influenced our results.

Compliance might provide an explanation for the contrasting results. The first two studies referred to above did not discuss this item, probably because it was not regarded as a problem.[13,14] One study[13] had a duration of 12 weeks in patients with chronic renal insufficiency, which condition may be of influence on compliance. The other study[14], however, resembled our study most, though duration of intervention was 6 months. The authors did not mention whether the study was performed under more controlled circumstances. Overall compliance in the third study, that took place in subjects with familial hypercholesterolemia, with a duration of 2 x 8 weeks using a placebo wash-out period of 4 weeks of prior lipid-lowering medication, was 90%.[15] Medication compliance in our study at the times of the various measurements ranged from 67% to 79% in both groups. The three daily doses of medication may be a factor for this suboptimal percentage, though this dosage scheme was also used in the other studies. In one study with antihypertensive medication, compliance improved from 59.0% in a three daily dose regimen to 83.6% in a one daily dose regimen.[24]

The MPPG and placebo groups showed the same drop-out pattern, without serious side effects that could be attributed to medication. Motivation, as characterized by the number of subjects leaving the study without announcement (table 8.5), dropped during the study. This may not be a specific feature of the present study. In a cross-national study in the United States and Canada measuring the persistence of the use of

lipid-lowering medications in patients older than 65 years, patients failed to fill prescriptions for about 40% for the study year.[25] In our study, the subjects' health status with respect to cardiovascular risk was discussed with the individuals at each visit to the GP, including the result of the previous TC measurement. The limited change in TC may thus have influenced the subjects' motivation. Side effects are an unlikely reason, since MPPG was generally well tolerated.

Statistical analyses have been executed on data in which missing values were substituted with the mean of the placebo at the corresponding time point. After exclusion of the missing values (not shown), very similar significance levels were found. However, it should be noted that except for TC and FB, laboratory assays were not standardized with other laboratories. The clinical-chemical variables (except cholesterol) were measured once at baseline, whereas these measurements may be prone to biological and analytical variance.

On the basis of our results, both the efficacy and effectiveness of MPPG are too poor to be of relevance for application as a lipid-lowering drug in general practice. When new studies are performed with lipid-lowering drugs in general practice, special attention should be given to compliance.

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Chapter 9

General discussion

9.1 Study objectives and subpopulations

The objectives of the Mierlo Project were to determine:

1. the influence of smoking on lipid and fibrinogen (FB) levels;
2. whether vital exhaustion is a risk factor for myocardial infarction (MI) and stroke;
3. whether magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) reduces total cholesterol, other lipid values and FB.

To meet these objectives, three subpopulations were selected and three separate main activities were undertaken in the field: the selection procedure, followed by the intervention study and, at a later stage, the determination of end points. This work resulted in two cross-sectional studies implemented during the selection procedure (at t_{-1}), in a hypercholesterolemic subpopulation with known clinical chemistry values (chapters 4 and 5). In addition, two prospective studies were performed in an older subpopulation, derived from the subpopulation of those patients taking part in the first examination of the selection procedure (at t_{-3}) who were administered the Maastricht Interview on Vital Exhaustion (MIVE; see appendix). These studies aimed to assess the extent of any vital exhaustion and thereafter to relate vital exhaustion to the end points of MI and first stroke (chapters 6 and 7). Finally, the selection procedure provided a hypercholesterolemic subpopulation, who participated in a randomized clinical trial (RCT; started at t_0) to investigate the efficacy and effectiveness of magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) as a lipid-lowering agent (chapter 8).

9.2 The selection procedure

The selection procedure represented a substantial part of the Mierlo Project, in terms of the time investment, logistics and organizational efforts it required. Since it would have imposed a major burden on the organizational system of the village health center, the project was organized outside the health center in a separate place specially equipped for this purpose, run by a practice-research nurse who had the necessary organizational skills.

The first step of the selection procedure involved the use of a

mailed questionnaire. This questionnaire had, however, not originally been designed for selection purposes, but to assess the modifiable risk of cardiovascular disease (CVD) among individuals in general practice.[1] It was found that the second question in particular (Does your father or mother or any of your brothers or sisters suffer from a cardiovascular disease or a high cholesterol level?) was non-selective and yielded a relatively large number of subjects who were not at risk. By contrast, question 3 (Do you suffer from diabetes?) hardly added any subjects, because, as might be expected, these diabetic subjects were already being monitored by the general practitioner (GP). This was also true for individuals who answered question 1 (Do you suffer from a cardiovascular disease?) affirmatively. Question 4 (Do you suffer from hypertension?) was confusing, since antihypertensive medication was not taken into account. Question 5 (Is your weight in kg more than your length in cm minus 100?) and question 6 (Do you smoke more than five cigarettes a day?) were suitable, as we found when we compared the answers with the assessments in the more detailed examination. Based on our findings (showing hypercholesterolemic subjects to be found mainly among the older women), it might have been worthwhile to include a question for women about their menopausal condition.

At t_{-3}, 4090 subjects were selected from the initial 5894 subjects (69%), of whom 515 were found to have a TC $\geq$ 7.0 mmol/l (9%). An evaluation of the selective power of the mail questionnaire with hindsight thus shows that this step resulted in a relatively large number of 'false positives' by using TC as a selection criterion. There were 973 subjects who answered all the questions in the negative (17%). This subpopulation may also have included 'false negatives'. If so, the number and power of the determinants from the two cross-sectional studies and the two prospective studies may have been underestimated.

Of the 4090 subjects at t_{-3}, 3514 were eligible to be assessed using the Coronary Risk Chart (CRC). This yielded an overview of the distribution of subjects at coronary risk in the Mierlo population, which may be of use in the debate on how to select and where to find individuals at risk in an apparently healthy population.

It is an intrinsic characteristic of the CRC that the great majority of subjects at high or very high risk will be found among smoking women $\geq$ 60 years and among all men $\geq$ 50 years (the four upper blocks for men

and the upper right block for women; see figure 3.1). The data of the Mierlo population show that in the subpopulation at t_3, 5% (11 out of 201) of the subjects at high or very high risk according to the CRC would have been missed if only smoking women ≥ 60 years and all men ≥ 50 years had been taken into. In fact, 11 of the total of 201 subjects at high or very high risk did not belong to these five blocks. The total number of subjects within these five blocks (i.e., smoking women ≥ 60 years and all men ≥ 50 years) was 526, of whom 190 (36%) were at high or very high risk. To identify the 36% subjects at high or very high risk in these 5 blocks, additional SBP and TC measurements were necessary.

Recently, *Wilson et al.* compared methods to identify individuals at increased CVD risk in a population similar to the Mierlo population, and concluded that *'[M]measuring the cholesterol concentration of everyone aged 50 years and over is a simple and efficient method of identifying people at high risk of coronary disease in the general population.'* [2] The authors defined 'at high risk of coronary disease' as a 10-year coronary event risk of 15% or greater. The CRC uses a higher risk limit, namely 20%. The age-based approach proposed by *Wilson et al.* means that in their study, TC measurements still had to be conducted in 2920 subjects (46%), with a yield of 93% of those at 15% or greater risk.

The decision to perform a screening procedure and to identify subjects at CVD risk depends mainly on cost-effectiveness considerations. Important questions in this respect are which parameters to use (age, gender, smoking habits, and the more labor-intensive SBP and TC measurements) and where to set the limits. The high-risk percentage limit is a criterion which is set at 20% in the 'European' CRC[3] and at 15% in the United Kingdom guidelines[2].

9.3 Smoking as a major risk factor for CVD

In studying risk factors for CVD, one inevitably persistently encounters the dominant role of smoking habits. This is also reflected in the CRC, in which smoking is a key variable. In the Mierlo population, the percentage of subjects at CVD risk was indeed considerably higher among smokers than among non-smokers.

As discussed in chapters 4 and 5, the results of the two studies on

the influence of smoking habits on LDL-C, HDL-C, TG and FB demonstrate the importance of smoking cessation for those who are already hypercholesterolemic. This is especially true in the hypercholesterolemic subpopulation, which is already at increased risk. In this subpopulation, smoking seemed to increase the CVD risk even more through its adverse influence on LDL-C, HDL-C, TG and FB, which underlines the assumption that CVD risk is multifactorial in nature. Moreover, non-smokers had much lower lipid and lipoprotein values than smokers, which may be an encouragement to stop smoking for the 28% of the total Mierlo population who reported smoking more than five cigarettes a day. The same seems to be true for the 30% of the total Dutch population who have this habit. Although many individuals find it hard to stop smoking, it remains the most important modifiable risk factor. This is also emphasized by our finding in the prospective study on stroke (chapter 7), in which stroke was 6.5 times more likely to occur in smokers than in non-smokers (p=0.004). For MI, we found an almost 100% risk increase (RR=1.97; 95% CI 0.95-4.08).

9.4 Vital exhaustion as a risk factor

Vital exhaustion reflects a breakdown of the body's adaptation to stress, and is a phenomenon more commonly observed in subjects with a low socioeconomic status.[3] Factors that may help explain this observation include exposure to environmental factors, like heavy work strain, lack of control over the work situation, lack of social support, as well as individual responses to stressors, the lack of capacity to cope with stressful factors encountered in life. These factors are often accompanied by an unhealthy lifestyle, involving smoking, poor dietary and exercise habits, and little health knowledge.

This large number of factors makes it difficult to establish a relationship between the standard risk factors and psychosocial factors. Fatigue, stress, and depression have been observed before and after MI, as well as after stroke, and depression is recognized as a risk factor for MI.[4] In the Mierlo Project, we used the concept of vital exhaustion, defined as a state of unusual fatigue, loss of energy, increased irritability and feelings of demoralization.[5] The distinction between depression and vital exhaustion remains a subject of debate.

Appels reported that most researchers agree on the symptoms that increase the risk of a first or recurrent cardiac event, but differ in their interpretation of these symptoms.[6] In his opinion, debates about the best definition for a combination of symptoms are seldom fruitful, as they often tell us more about the point of view from which an investigator explores the area than about the observations themselves. In the present case, however, the debate is important because of its implications for treatment, and thus for the inclusion of this behavioral factor in the preventive activities of GP's. If the symptoms of unusual fatigue, lack of energy, increased irritability and malaise reflect a mental disorder, treatment should be provided by psychotherapists. If, on the other hand, the symptoms reflect a normal reaction to abnormal conditions, the treatment should not address the symptoms as a form of psychopathology and, consequently, could be provided by highly trained nurses or trained health advisors (see 9.6 Practicability). Although the Mierlo study does not contribute to the debate whether the symptoms are best approached as depression or as a state of exhaustion, its results support the belief that the factor covered by the questions of the Maastricht Interview on Vital Exhaustion (MIVE) belongs to the risk factors for MI and stroke.

It has been reported that depression is related to CVD risk, and is partly independent of the standard risk factors.[5] Using the CRC, which includes the variables of age, gender, smoking habits, systolic blood pressure (SBP), and TC, we found that only 5% of the subjects with vital exhaustion were at high or very high risk, confirming a low correlation between vital exhaustion and the standard risk factors. Nevertheless, we found vital exhaustion to be more predictive of MI than standard risk factors like age, gender, SBP, TC, smoking, and diabetes mellitus (DM) (chapter 6). As chapter 7 reports, vital exhaustion was also more predictive of stroke than age, gender, diastolic blood pressure, SBP or body mass index (whereas TC, DM, and smoking were more predictive).

Since psychosocial factors have been much less extensively researched than the standard risk factors for CVD, it is understandable that these factors are not mentioned in the Practice Guidelines of the Dutch College of General Practitioners (NHG) on CVD risk.[7,8] This may well change in the future, however, since the recent *Second national study into diseases and actions in general practice*[9] has established that (chronic) fatigue is a serious health factor in the general Dutch population.[10] The researchers

mention that fatigue is embedded in a much broader range of health problems. They state that '[T]he word *'epidemic'* seems to be appropriate'. In the Second national study, 4416 women and 3708 men, aged between 15 and 64 years, were asked the question 'have you felt fatigued in the last two weeks before the interview'. Fifty percent of the women and 33% of the men reported being fatigued (> 40% in all, versus 29% fifteen years ago).

Since the designs of the Mierlo Project and the national study were different, any comparison should be made with caution. Nevertheless, we found an important result, which was similar to that of the national study, namely that relatively more women than men were fatigued/exhausted.

The national study reported that 56% of all women who had visited their GP in the last two months complained about fatigue.[9] This high percentage underlines the need to address this problem. Therefore one of the purposes of the national study was to decide upon the best approach for GPs when confronted with patients complaining of fatigue. Differential diagnosis between the various forms of fatigue is highly recommended, and the MIVE may be a useful instrument for this purpose. Another complicating factor is the problem of treatment, although new instructions for GPs on the diagnosis and treatment of fatigue are now available.[9] The link with CVD risk found in the Mierlo Project may accelerate the growth of awareness of the importance of this problem.

The Mierlo Project included two prospective studies of the relation between vital exhaustion and CVD risk, each with a relatively short follow-up period. We recommend extending this follow-up in the same subpopulation, especially since vital exhaustion represents a new approach to CVD risk. This may also be an incentive for the NHG to start research in this field, with the ultimate aim of developing recommendations for GPs on how to address these problems.

9.5 Efficacy and effectiveness of MPPG in relation to medication compliance

We found that MPPG, used in a primary care setting, is not valuable as a lipid-lowering agent. Its efficacy and effectiveness were poor.

Previous human studies with MPPG, including two carefully designed double-blind, placebo-controlled studies (RCTs) found a favorable

effect of MPPG on TC, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides (TG).[11,12] The most recent study[13], however, failed to confirm these results, as did our RCT. Neither the authors nor we were able to provide an adequate explanation for the divergent results.

The fact that MPPG has hardly any adverse effects could have been an argument in favor of the use of MPPG in the treatment of dislipidemia in general practice, in particular additionally to the HMG CoA reductase inhibitors (statins), especially because of MPPG's previously found TG-lowering effect, which is hardly exerted by the statins. However, its lack of efficacy makes it less relevant.

In our study, MPPG showed poor effectiveness. The main components of effectiveness are compliance and attitude towards preventive measures, among patients as well as GPs. These are delicate factors in lowering cardiovascular risk in primary care and may therefore not apply exclusively to MPPG, but may also be true for the role of statins in cholesterol treatment in primary care. In general, patient compliance plays a prominent role in lowering TC levels in patients without any inconvenient symptoms.

In our study, total drop-out (MPPG and placebo) was 35%, most of it in the first months of the intervention. Subjects simply did not show up at the scheduled visit to the GP or the scheduled blood sampling, despite repeated attempts to convince them to continue their participation. Medication non-compliance was also considerable in both groups, ranging from 67 to 79% of those still participating, with no significant differences between the MPPG and placebo populations.

The latter effect might have been due to the fact that the subjects' health status with respect to cardiovascular risk, including the result of the previous TC measurement, was discussed with the individuals at each visit to the GP. The relatively limited change in TC between two consecutive visits might thus have reduced the subjects' motivation. However, in a non-drug randomized study in five general practices, this effect seemed to be negligible.[14] In this study, advice to reduce dietary fat intake and to stop smoking was given by practice nurses during health checks. Both groups were given the same advice, but the intervention group was also given immediate feedback on their cholesterol concentration. The mean drop in TC levels did not differ significantly between the two groups.

Another factor that may have affected compliance in our study was the fact that the medication had to be taken three times daily. In one study with antihypertensive medication, compliance improved from 59% in a three times daily doses regimen to 84% in a once daily regimen.[15] However, the literature shows that compliance is a general problem in cholesterol-lowering treatment, and not a problem of our study in particular. For example, in a cross-national study in the United States and Canada measuring persistence in the use of lipid-lowering medications during one year in patients older than 65 years, patients did not adhere to the dosage regimen for about 40% of the study year.[16] Over a period of five years, no more than half of the surviving US population persisted in using the lipid-lowering medication.

This is confirmed by the observations in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Trial (ALLHAT-LLT).[17] In this study pravastatin, which has been proven to be an effective cholesterol-lowering agent, did not significantly reduce either all-cause mortality or coronary heart disease (CHD), compared with usual care, in older participants with well-controlled hypertension and moderately elevated LDL-C.

Pasternak suggested in his accompanying editorial[18] that what may have happened is that the drugs may not be as effective in ordinary settings as they are in RCTs, where participants are carefully selected and followed closely. He referred to two other studies that documented very poor persistence in the use of statins within six months after the initiation of therapy.[19,20] Compared to patients with acute coronary syndrome, adherence rates were significantly lower in those with chronic coronary artery disease (RR 1.14; 95% CI, 1.11-1.16) and in those without coronary disease (primary prevention) (RR 1.92; 95% CI, 1.87-1.96).[19] In a large Scottish study, only 7.7% of patients who had had an MI adhered to their statin therapy.[21] Those whose statin compliance was less than 80% showed no significant reduction in MI recurrence or all cause mortality. Compliance with statin therapy in the long run has been studied in an elderly US population (65 years of age and older, until death).[20] It was concluded that persistence with statin therapy in older patients declined substantially over time (five years), with the greatest drop occurring in the first six months of treatment. This observation is in agreement with our findings regarding MPPG.

In England, lipid concentrations and the use of lipid-lowering drugs in primary care have been studied in a national cross-sectional survey using a representative sample.[22] Despite the high prevalence of dislipidemia in English adults, the proportion of adults taking lipid-lowering drugs in 1998 was only 2.2%. Rates of treatment were low among high-risk patients eligible for primary prevention with lipid-lowering drugs, and less than one-third of patients with established CVD received such treatment.

The authors wondered why rates of treatment remained low, despite the proven huge beneficial effects of statins. The accompanying editorial[23] mentioned various factors. Besides some practical factors (the initial lack of known efficacy of statins in the nineties, lack of sufficient funding and support by the National Health Service, concerns over the safety of lipid-lowering drugs), these also included factors relating to the attitudes of patients and GPs. With regard to patients, the editorial mentioned the lack of compliance and the inverse care law, that is, the phenomenon that those who are at high risk do not seek treatment, and those at low risk do (this is discussed in more detail below[24]).

Most of the problems mentioned are in agreement with our own experience of lowering TC levels in primary care. Additionally, as has been shown in the REACT survey[25], performed in five European countries (France, Germany, Italy, Sweden and the UK), GPs may overestimate their patients' knowledge about cholesterol as a risk factor for CHD. Only 45% of the subjects were aware that CHD is the main cause of death while 51% knew that hypercholesterolemia increases the CHD risk. There was no difference in risk perceptions between subjects with CVD or with risk factors and those without disease.

9.6 Primary prevention: not a GP's task?

Knowledge of risk factors

Prevention is better than cure, especially now that the average life expectancy in the Netherlands has risen to about eighty years, increasing the risk of degenerative diseases in the final stages of life. Hence, society is attaching great value to prevention, which should preferably start at the earliest possible age.

The choice of cardiovascular diseases as a target for primary prevention is obvious, as cardiovascular diseases are the main cause of morbidity and mortality in the Western world, including the Netherlands. In addition, scientific research has greatly increased our knowledge of the etiology and epidemiology of these diseases. While familial factors obviously play a major role, the Western lifestyle is such that behavioral factors, ranging from dietary and exercise habits to psychosocial factors, are major elements in the high morbidity and mortality rates from cardiovascular diseases. Since the late 1940s, research has tried to identify factors affecting the risk of cardiovascular diseases, the most publicized and most influential probably being the Framingham Heart Study, which started in 1948. Even today, many studies are still in progress to examine relations between life-style factors and cardiovascular diseases, like the Atherosclerosis Risk in Communities Study (ARIC study), the Physicians' Health Study, the Nurses' Health Study and the Lyon Diet Heart Study, to name but a few. Over the years, science has provided us with accurate and detailed information on factors increasing the risk of cardiovascular diseases and, in consequence, on factors reducing the risk of such diseases.

Some 200 major and minor risk factors have now been identified[26], with smoking, hypertension and elevated cholesterol levels currently being regarded as the main modifiable factors. New risk factors and risk indicators are still being discovered, including hyperhomocysteinemia[27], C-reactive protein[28] and, as the Mierlo Project has confirmed, vital exhaustion. Overweight is also being increasingly recognized as a condition that greatly impacts on society and that imposes and will continue to impose a major burden on the health care system.[29,30] Overweight, resulting from an imbalance between excessive (and unhealthy) dietary intake on the one hand and lack of exercise on the other, is closely related to hypertension, hypercholesterolemia and diabetes mellitus (DM), which are generally accepted to be risk factors for cardiovascular disease.

The 'Preventie: maatwerk' (tailored prevention) project

With the information on risk factors now being available, the question arises how to implement this knowledge in a societal context. The way the Dutch health care system works is that GPs are normally the

first point of contact for individuals who feel ill. It is therefore not surprising that GPs are often seen as the most obvious professionals to deal with primary prevention.[31] Hence, Dutch GPs have asked themselves how the available knowledge of cardiovascular risk factors can be utilized to reduce morbidity and mortality rates from such conditions. The NHG has therefore developed guidelines, based on research findings, to help GPs assess and combat risk factors and treat any conditions resulting from these factors.[7,8] However, after the practice guidelines had been developed, the next hurdle was obviously to implement them.

In 1992, the Dutch Association of General Practitioners (LHV) and the NHG formulated three criteria that preventive activities had to meet to be eligible for systematic implementation in general practice:[31]

1. the activity must be meaningful;
2. the activity must fit in with the GP's tasks;
3. the activity must be practicable.

After the LHV and NHG had come to the conclusion that cardiovascular prevention did meet these three criteria, a pilot project was started on 1 January 1998. Since the government agreed that this was indeed a GP's task, the Ministry of Health, Welfare and Sport funded the project. About 15% of all Dutch GPs participated (the intention being that the others would become involved at a later stage). The project, which was given the name 'Preventie: maatwerk' (tailored prevention), involved the creation of support teams, which included prevention consultants, as well as the development of written materials and training courses. The main component of the project was screening the population and registering cardiovascular risk factors, initially only among those aged 60 or over.

At the end of the project, one of the organizers characterized it as 'a success story without a happy ending'[32], for although the results of this screening and registration project were favorably evaluated, an LHV meeting in 2000 rejected its continuation.[33] The reasons were apparently political and strategic, arguments being basically that, at the time, GPs were under great pressure of work (because of the national shortage of GPs relative to the number of patients) and generally regarded their remuneration as inadequate.

It had to be concluded that there was insufficient support for implementing the project on a larger scale (to include the remaining GPs) and to extend it to include intervention. Two GPs had already expressed

doubts about the value of systematic cardiovascular prevention in general practice previously[34], their arguments being based mostly on the 1997 meta-analysis by *Ebrahim and Davey Smith*.[35] The latter had reviewed all qualitatively adequate intervention studies on multiple cardiovascular risk factors held among general practice and workplace populations between 1966 and 1995. The meta-analysis, with a combined observation period of 900,000 person years, found no reduction in cardiovascular mortality.

The two Dutch GPs[34] calculated that, in view of general practice sizes in the Netherlands and the time required for primary prevention measures, implementation in the Dutch situation would imply a huge increase in time investment and costs. They concluded that the project did not meet the criteria of meaningfulness and practicability. As regards the second criterion – is it a GP's task – the two GPs contended that few GPs actually felt primary prevention to be part of their task, since 'doctors treat patients, not populations', a statement derived from the title of a review of the prevention of mild hypertension, which preferred individual patient care over large-scale prevention.

The 'Hartslag Limburg' (Limburg Heartbeat) project

Another Dutch project involving primary prevention is that of 'Hartslag Limburg' (Limburg Heartbeat, named after the Dutch province of Limburg).[37] This project aimed to achieve favorable lifestyle changes among the population of the town of Maastricht and four neighboring villages by means of a total prevention strategy, involving not only GPs but various other relevant experts as well. The project involved creating a new type of expert, the 'health advisor', who is a health expert and is able to evaluate participants' health risks and support GPs and cardiologists in their health counseling tasks. These health advisors hold a key position in one of the project's two subprojects, which is known as the 'High Risk Project' and has 2700 participants recruited from the outpatient clinic at the University Hospital of Maastricht and from 35 GPs (in 19 practices). The health advisor acts as the linchpin in the project and mediates between doctors and participants. This 'High Risk Project' was designed a randomized controlled study with the intention of examining the effect of the health advisors' activities on cardiovascular morbidity and mortality rates. Of the

approximately 2700 participants, about 15% are healthy but are subject to one or more risk factors. This means that the 'Hartslag Limburg' project is comparable to the Mierlo Project in the sense that it involves primary prevention.

The second subproject, besides the 'High Risk Project', is the so-called 'Community Project', which includes 180,000 participants and intends to achieve favorable lifestyle changes among the total population by means of a public strategy. It targets particularly the lower income groups. The design of the project as a whole implies that the two subprojects overlap, and that the Maastricht local health authority plays a key role in the project.

The 'Hartslag Limburg' project, which is one of the twelve projects selected by the WHO for inclusion in its 'Towards Unity for Health' (TUFH) project, was started in 1998. Its final results are expected to be reported in 2003.

The Mierlo Project and primary prevention

Do the experiences gained with the Mierlo Project and the two projects discussed above allow any conclusions to be drawn about primary prevention in terms of the criteria of 'meaningfulness', 'being part of a GP's task' and 'practicability'? The Mierlo Project involved one health center with five GPs, screened almost 6000 persons aged between 26 and 66, and implemented a drug intervention lasting (only) one year among approximately 200 hypercholesterolemic persons. Many of its activities, including the entire screening procedure, took place at a selection center, located away from the health center and run by an experienced practice-research nurse. The next sections discuss each of the three LHV and NHG criteria[31] for implementing primary prevention in general practice.

Is prevention meaningful?

Primary prevention is only meaningful if interventions can be successfully implemented after the screening procedure and results can

be reported. The 'Preventie: maatwerk' project never got to this stage, while the Mierlo Project did achieve this, though only for one year and only for a cholesterol-lowering agent. Although the participants to the Mierlo Project were enthusiastic about participation in the screening procedure (as they wanted to know their data), they were less eager to participate in the intervention: 22% of the subjects who had an elevated cholesterol level and no exclusion factors nevertheless refused to participate in the clinical trial. In addition, implementing the cholesterol-lowering intervention turned out to be a difficult process, mostly because of compliance problems (see 9.5). Although this lack of compliance was naturally aggravated by the lack of efficacy of the drug, it must be said that compliance, and hence an intervention's effectiveness, is generally problematic in such prevention trials. In this sense, the Mierlo project was no exception.

Whether primary prevention is meaningful also depends on the degree of 'inverse care', the phenomenon that 'the availability of good medical care tends to vary inversely with the need for it in the population served.'[24] In other words, those who would benefit most from primary prevention are often not reached. This phenomenon is particularly relevant in primary intervention, which asks individuals, for instance, to take antihypertensive or cholesterol-lowering medication every day even though they have no symptoms. This requires high levels of health consciousness and motivation. Research has shown that people's awareness of their own health status is generally poor. For instance, 20% of the working population in the United States claim to be in excellent health even though they are overweight, smoke, drink too much alcohol and never engage in exercise.[38] And a study by NFO Trendbox showed that 78% of the Dutch population are unaware of their own cholesterol level.[39] A certain amount of knowledge about one's own health status is an important pillar of primary prevention, and is also an indication of people's willingness to do something about their own health. This makes research into the 'inverse care' effect a major factor in assessing the meaningfulness of primary prevention. Furthermore, the value of any form of medical intervention, including primary prevention, is nowadays also being assessed in terms of cost-effectiveness considerations, an aspect which is also being evaluated in the 'Hartslag Limburg' project.[37]

Unlike the standard risk factors of hypercholesterolemia and hypertension,

which are symptomless, vital exhaustion is an observable discomfort and a complaint that people would like to see treated. This is why exhausted patients present to the GP, and it means that their motivation to comply with therapy to alleviate the problem is high. Thus, the problems of identification, compliance and 'inverse care' are intrinsically much smaller for vital exhaustion than for hypercholesterolemia and hypertension.

A GP's task?

As reported above, screening in the Mierlo Project was done at a separate selection center located away from the health center. From an organizational point of view, the selection procedure went smoothly. The intervention part of the project consisted of six visits to the GPs, which included a brief discussion of the person's problems and renewal of the prescription for the study medication every three months. Blood samples for clinical chemistry assessment were taken at the selection center, and the MIVE interviews to assess vital exhaustion were also held there.

The presence of the GPs was not strictly required for any of these activities, although the trust between doctor and patient may well provide added value, especially in treating vital exhaustion. It is unknown to what extent this special relationship affects the outcome of primary prevention. At any rate, compliance with the cholesterollowering agent in the Mierlo Project proved poor.

A general comment that can be made here is that many of the components of primary prevention are, by definition, not part of the GP's task, since he or she is not trained for them. The screening procedure, for instance, is largely an organizational activity. While such a screening procedure should preferably be carried out in a medical setting, it does not have to be implemented by a GP.

Interventions involve influencing behavior – to treat vital exhaustion or to change smoking, dietary and exercise habits – as a separate activity, requiring expertise that GPs do not necessarily possess. This activity could also be delegated to experts like psychologists, dieticians or fitness trainers. The 'Preventie: maatwerk' (tailored prevention) project, for instance, employed prevention counselors, while the 'Hartslag Limburg' (Limburg Heartbeat) project used health advisors.

Practicability

The third criterion relates to the practicability of primary prevention. Like the 'Preventie: maatwerk' project, the Mierlo Project also found that primary prevention was an organizational challenge, particularly the screening procedure. Nevertheless, the Mierlo Project was successful (with 91% of the population returning the questionnaire and 5% of these refusing further participation). The Mierlo Project drew considerable attention in the village. Local newspapers and magazines publicized it, and the project was a common conversation topic among the villagers. In view of the considerable organizational effort and expertise required for the screening procedure, the project was implemented at a special selection center, as the health center was insufficiently equipped to deal with this. All appointments, including those for participants visiting the GP during the intervention, had to be made from the selection center, which also took care of taking and processing blood samples for lipid screening.

We have already touched upon the aspect of behavioral modification during the intervention implemented by the GPs. Quite apart from the question whether GPs are qualified for this task, it should be stressed that this is a very time-consuming matter, which requires long-term counseling. It is questionable whether this is feasible with a general practice setting. If the problem is vital exhaustion, certain methods are available to ameliorate feelings of exhaustion. The problem could be addressed by self-help groups with expert supervision. The supervisors could be highly trained specialist nurses or health advisors like those involved in the 'Hartslag Limburg' (Limburg Heartbeat) project after a specialized additional training. In any case, addressing mental factors in projects like 'Hartslag Limburg' would mean a major improvement.

Apart from treating patients who present to the GP with vital exhaustion, the simplest and most effective method of implementing primary prevention may be to screen for and intervene in smoking habits, as those at greatest risk are to be found among smokers, who are moreover easy to identify. Some research findings have indicated that interventions by the GP in this respect are indeed effective.[40,41] At the same time, however, it may be questioned whether smoking habits could not just as well be addressed by other experts, whether or not in a medical setting. Concentrating primary prevention efforts on smokers would avoid organizationally

complex, expensive and laborious screening procedures, hence greatly enhancing practicability. Such strategies concentrating on high-risk groups could then be supplemented by population strategies, as is being done in the 'Hartslag Limburg' project. Nevertheless, this strategy also needs to pay attention to what may well be the most important factor: individual motivation to participate in primary prevention.

Individual motivation

In addition to the three criteria (meaningfulness, being part of a GP's task and practicability) set by LHV and NHG[41], a fourth criteria would seem to be important, one which precedes the other three: the individual's willingness to engage in primary prevention. The recent third revision of the NHG Practice Guideline on Hypertension expresses this as follows[8]: *'Where possible, the GP should decide upon a treatment policy in consultation with the patient, taking into account the latter's specific circumstances and recognizing the patient's own responsibility, conditional upon adequate patient education.'* The debate initiated by the 'Preventie: maatwerk' (tailored prevention) project and the experience gained in the Mierlo Project justify the addition of these aspects of individual motivation and each person's own responsibility. This is underlined by the finding that it was very difficult to persuade participants to take three tablets a day, which were provided free of charge, even though this is perhaps the easiest form of prevention imaginable, much easier than smoking cessation, more exercise or a healthier diet.

Although in surveys, most Dutch people claim that their health is their most precious possession, this is not always borne out in actual practice. Only 1.8% of the Dutch population have a diet that corresponds to the dietary guidelines provided by the Dutch Gezondheidsraad (Health Council).[42] Also, Dutch people take too little exercise, and about 30% continue to smoke[43], although there is a general awareness that smoking seriously damages their health.

There are apparently factors at work which induce Dutch people to attach just as great a significance, if not greater significance, to values other than health, including family life, professional life, social contacts, gathering possessions, recreation, creativity and pleasure, to name but a

few. In everyday life, each individual regularly decides, consciously or unconsciously, what level of priority to assign to each of these values, and health may not necessarily always come out on top. In fact, people have to decide for themselves what order of priorities they prefer. There may be situations in which these values may be complementary, but also situations in which one value has to be traded off against another. Health status may be achieved at the expense of a busy job or an ambitious career planning. In addition, people may, through no fault of their own, end up in situations that endanger their health. This makes the idea of primary prevention even more remote to them.

What is lacking in the literature, as well as in the Mierlo Project, the 'Preventie: maatwerk'[31] project and the 'Hartslag Limburg'[37] project is a method to measure individual motivation to collaborate in primary prevention in relation to the other aspects of life referred to above. This relates directly to the question how much time and effort an individual is willing to allocate to primary prevention. Whereas participation in scientific research projects on primary prevention is always free of charge, the costs factor is a crucial variable and excluding it from studies may result in the predictive value of other risk factors being overestimated. It would seem preferable, therefore, to include the costs factor as an independent variable in any study involving human behavior as a factor.

9.7 Final conclusion

The Mierlo Project studied risk factors for cardiovascular diseases in a primary care population, their interrelationships, clinical outcomes and responses to intervention.

As regards the standard risk factors (hypercholesterolemia, hypertension, and smoking), this project confirmed the importance of smoking habits. In the Mierlo population, the majority of subjects at high or very high risk were found among smokers. In addition, smoking had an aggravating effect on lipid and FB values in hypercholesterolemic subjects. Although smoking cessation remains hard for many subjects, it may be the most effective method to decrease CVD risk in individuals as well as in populations. Moreover, smokers are easy to detect.

Interventions on hypercholesterolemia and hypertension may seem

a less complicated method to decrease CVD risk in individuals and populations, because of the availability of effective medication. However, the effectiveness of interventions on these factors is questionable. A lack of symptoms associated with these risk factors contribute to poor compliance, as has been observed in the RCT part of the Mierlo Project. Moreover, influencing the behavior of subjects with hypercholesterolemia and hypertension also remains a delicate problem, since the underlying factors of these risk factors include poor lifestyle, involving aspects like unhealthy diet, lack of exercise and, again, smoking.

A new, supplementary approach which is supported by the findings of the Mierlo Project is to use vital exhaustion as a risk indicator. The Maastricht Interview on Vital Exhaustion (MIVE) could be used as an instrument to distinguish between vital exhaustion and other forms of fatigue. The Mierlo Project has shown that vital exhaustion predisposes people to myocardial infarction and first stroke, which together constitute by far the most important causes of morbidity and mortality in the Netherlands. People suffering from vital exhaustion are likely to present to the GP, which means that its detection does not require a laborious and expensive screening program, while the risk of an 'inverse care' effect is small. It therefore seems useful to design a research project examining methods to assist people showing signs of undue strain as well as cardiovascular problems. Such a project could use the research design of the 'Hartslag Limburg' (Limburg Heartbeat) project as a model, including the division of tasks between the GP and other experts.

Reducing the risk of cardiovascular disease in a population may benefit from granting a major role to such a strategy to combat vital exhaustion, in addition to the standard risk factors, above all smoking.

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SUMMARY

This thesis describes the Mierlo Project, which studied risk factors for cardiovascular disease (CVD) in a primary care population, with their interrelationships, clinical outcomes and responses to intervention.

Awareness of risk factors is an important prerequisite for primary prevention. The Framingham Heart Study, started in 1948, has contributed greatly to our understanding of the significance of risk indicators for CVD. Generally recognized risk factors currently include older age, male gender, positive family history, habitual smoking, hypertension, diabetes mellitus (DM), elevated total cholesterol (TC) and abnormal related lipid parameters, and an elevated fibrinogen (FB) level. New risk indicators and risk factors are still being identified, one of the recently discovered ones being vital exhaustion.

In the Netherlands, identification and counseling of subjects at CVD risk are part of the daily general practice routine. In recent years, experts have started to develop workable models to optimize CVD-preventive care in general practice. In 1998, this led to the start of the 'Preventie: maatwerk' (tailored prevention) project, an initiative of the Dutch College of General Practitioners (NHG) and the National Association of General Practitioners (LHV), and of the 'Hartslag Limburg' (Limburg heartbeat) project, a project within the framework of WHO's 'Towards Unity for Health' project. General practitioners (GPs) play a major role in both approaches.

The Mierlo Project also addressed various aspects of CVD risk in a primary care setting. Its objectives were formulated in **chapter 1** of the present thesis as follows:

1. to determine the influence of smoking on low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and FB in a hypercholesterolemic subpopulation;
2. to determine whether vital exhaustion is a risk factor for myocardial infarction (MI) and first stroke;
3. to determine whether the drug magnesium-pyridoxal-5'-phosphate-glutamate (MPPG) influences total cholesterol (TC), LDL-C, HDL-C, TG, apolipoprotein-A1 (Apo-A1), apolipoprotein-B100 (Apo-B), lipoprotein a [Lp(a), secondary] and FB.

Chapter 1 discusses general issues concerning risk factors, particularly in relation to the relevance of primary prevention in general practice, and reports the above objectives of the Mierlo Project. Chapter 2

describes the design and setting of the Mierlo Project, while chapter 3 summarizes the characteristics of the study population. Chapters 4 to 8 describe the five studies which have been performed as part of the Mierlo Project: two cross-sectional cohort studies (chapters 4 and 5) on the interrelationships between smoking and clinical chemistry values in hypercholesterolemic subjects; two prospective studies (chapters 6 and 7), investigating whether vital exhaustion is a risk factor for MI and stroke, and an intervention study (chapter 8) investigating the effect of MPPG on clinical chemistry values. Chapter 9 discusses what the findings of the Mierlo Project may mean for primary CVD prevention in general practice, particularly for the Dutch situation.

The project was implemented in the Dutch village of Mierlo, as described in **chapter 2**. The population of this village may be assumed to have the characteristics of an average, though not representative, West-European population. Mierlo is a village with approximately 10,000 inhabitants, 15 km south-east of Eindhoven (in the southern part of the Netherlands). In this village, five GPs collaborate in one health center. For the purpose of the Mierlo project, a special location was set up, separated from the health center, where the selection procedure took place and from which the project was coordinated. At this selection center, one experienced practice-research nurse and one specifically trained research nurse were responsible for the logistics (mailings, making appointments, transportation of blood samples) and the measurement of blood pressure and the anthropometric parameters of height and weight. They performed the blood sampling and also asked the subjects about their lifestyle habits, like smoking.

The table shows the main components of the Mierlo Project, the actions undertaken and the numbers of subjects who were involved in the consecutive steps. The first step of the selection procedure involved compiling a database of 5894 adults, derived from the municipal register and aged between 26 and 66 years. These subjects received a mailing with a simple questionnaire about factors related to CVD:

1. Do you suffer from a cardiovascular disease?
2. Does your father or mother, or any of your brothers or sisters suffer from a cardiovascular disease, or a high cholesterol level?
3. Do you suffer from diabetes?
4. Do you suffer from hypertension?

Table. Mierlo Project flow chart showing the three main components, the actions undertaken and the population, aged between 26 and 66 years. In the course of the various steps, subjects dropped out for various reasons (refused participation, moved, died or did not qualify).

Component	action	number (%)	
Selection	Registered, questionnaire mailed	5894 (100)	
	Returned questionnaires	5368 (91)	
	All 6 questions 'no'	973 (17)	
	At least one question 'yes'	4395 (75)	
	First screening	4090 (69)	
	MIVE subpopulation: 41-66 years	2433 (41)	Studies described in chapters 6 and 7
	Second screening	506 (9)	
	Third screening	492 (8)	Studies described in chapters 4 and 5
Intervention	Clinical trial with MPPG	202 (3)	Study described in chapter 8
End point assessment	Cases with MI and/or first stroke	2433 (41)	Studies described in chapters 6 and 7

MIVE subpopulation: subjects who underwent the Maastricht Interview Vital Exhaustion
MPPG: magnesium-pyridoxal-5'-phosphate-glutamate MI: myocardial infarction

5. Is your weight in kg more than your length in cm minus 100?
6. Do you smoke more than 5 cigarettes a day?

If one or more of the questions on the returned questionnaire had been answered affirmatively, the respondent was invited for the first visit to the selection center, which consisted of a further examination: assessment of TC, diastolic blood pressure (DBP) and systolic blood pressure (SBP) and height and weight measurements. Subjects who were aged between 41 and 66 years were administered the 'Maastricht Interview on Vital Exhaustion' (MIVE), consisting of 23 questions asking about unusual fatigue, loss of energy, increased irritability and feelings of demoralization (appendix). All subjects with TC ≥ 7.0 mmol/l were invited for a second and a third visit with approximately the same procedures as the first visit (except for the MIVE procedure). At the third visit, the staff also determined LDL-C, HDL-C, TG, Apo-A1, Apo-B, Lp(a) and FB.

The intervention consisted of a clinical trial with the lipid-lowering agent MPPG versus placebo. Of the 492 subjects with TC ≥ 7.0 mmol/l at the third screening, 202 finally participated in the trial. In 112 of the 492

subjects, the mean TC (of the three consecutive TC measurements) was found to be below 7.0 mmol/l, causing them to be excluded. The other reasons for exclusion were mainly not meeting the inclusion criteria (n=116) and refusal to participate (n=54). The intervention lasted for one year, during which six GP visits took place. The procedure for the follow-up visits to the GP was approximately identical to that at the second and third visits at the selection center.

End points for vital exhaustion were determined approximately fifty months after the first visit at the selection center. The GP's medical records were used to determine if a subject in the MIVE subpopulation had suffered an MI and/or first stroke.

Chapter 3 provides a more detailed description of the study population and the various subpopulations. Compared to available figures on the general Dutch population, the Mierlo study population did not appear to differ much in terms of the prevalence of hypertension, DM, overweight, or smoking habits.

For the majority of the subpopulation at the first screening (n=3514), we established the risk of coronary heart disease (CHD) according to the Coronary Risk Chart (CRC). This chart allows a simple CHD risk estimate to be made for an individual on the basis of the variables age, gender, smoking habits, TC levels, and SBP. Healthy high-risk individuals are defined as those whose 10-year CHD risk exceeds 20%. In our subpopulation, this category included mostly smokers (66%), of whom 77% were men. Applying the CRC to the MIVE subpopulation showed that 5% of the exhausted subjects were at high risk, mainly women (9%, versus 5% of the men), evenly distributed among smokers and non-smokers.

The two cross-sectional studies were performed among participants found to be hypercholesterolemic at the third examination. This subpopulation was divided into four subgroups, based on age and gender (men < 50 y, men ≥ 50 y, women < 50y, women ≥ 50 y). The cohort included 492 subjects with an initial TC level ≥ 7.0 mmol/l.

Chapter 4 describes the relation between smoking habits and LDL-C, HDL-C, and TG. Relative differences between smokers and non-smokers in the mean values of TC, LDL-C, HDL-C, and TG were 2.2%, 5.5%, -8.1%, and 13.7%, respectively. Over the entire cohort, including men and women, age did not affect the mean values significantly, except for TC and TG values in smoking women, which were significantly higher in women

over 50 than in the younger women. It was concluded that smoking is not only a CVD risk factor in itself, but may increase the CVD risk even more in a hypercholesterolemic population, through its adverse influence on LDL-C, HDL-C, and TG levels. Smoking cessation may be even more effective in reducing CVD risk in hypercholesterolemic men and women, of all ages, than in normocholesterolemic subjects.

Chapter 5 discusses the relation between smoking habits and FB. Mean FB levels among smokers and non-smokers in the four subpopulations (men < 50 y, men ≥ 50 y, women < 50y, women ≥ 50 y) followed mean TC levels. Three subpopulations showed differences in mean TC and FB values between smokers and non-smokers of 2.4 (not significant) and 15.8%, respectively, in men < 50 y, of 4.6 and 18.3%, respectively, in men ≥ 50 y and of 3.2 and 8.8%, respectively, in women ≥ 50 y. No differences between smokers and non-smokers were observed in the younger female group (< 50 y). Smokers in the latter group had strikingly low FB levels. A similar result was found for the TG level in the other cross-sectional study, which was found to be 12% lower among smoking younger women than among non-smoking younger women, although the difference was not significant. No explanation could be found for these two low values. In conclusion, the effect of smoking on FB was much stronger than on TC. Smoking may also be a risk factor for CVD by exerting an effect on FB.

It is known that fatigue is a common condition after MI and stroke. In the case of MI, this state already exists before the event. Vital exhaustion is defined as a state characterized by unusual fatigue, loss of energy, increased irritability, and feelings of demoralization. This observation induced us to conduct two prospective studies to establish the predictive value of vital exhaustion for MI and first stroke.

The Maastricht Interview on Vital Exhaustion (MIVE: see appendix) was used to assess vital exhaustion in a subpopulation (n=2433), aged between 41 and 66 years, from the first screening. Other CVD risk factors established were age, gender, SBP and DBP, TC, body mass index (BMI), smoking habits, existing CVD, and DM. The end points of MI (fatal and non-fatal MI) and first stroke were determined a median of 50.8 months later.

Chapter 6 discusses the predictive value of vital exhaustion for MI. At the univariate level, vital exhaustion was found to double the risk of

MI (RR=2.54; 95% CI 0.97-6.64). The effect of exhaustion was confounded by gender, with women having higher exhaustion scores and a lower incidence of MI. Controlling for gender, age, SBP, TC, smoking habits, existing CVD, and DM, vital exhaustion almost tripled the risk of MI (RR=2.91; 95% CI 1.07-7.92). Of the other determinants, only existing CVD yielded a higher risk (RR=3.51; 95% CI 1.57-7.86). It was concluded that assessment of vital exhaustion contributes to the identification of subjects at increased risk of MI in general practice.

Chapter 7 describes a study undertaken to examine whether vital exhaustion is a precursor of first stroke, while controlling for other CVD risk factors. Vital exhaustion increased the risk of stroke by 13% per point on the MIVE (p=0.003). This figure remained statistically significant and hardly changed upon correction for other risk factors. It was concluded that a state of exhaustion is one of the risk indicators of first stroke. This means that the fatigue so often seen after stroke was already experienced by many patients before the occurrence of the stroke.

Chapter 8 reports on the clinical trial with MPPG. This randomized double-blind, placebo-controled, clinical trial lasted 12 months and was performed in a general practice setting. The objective was to assess the efficacy and clinical effectiveness of MPPG in modifying TC, LDL-C, HDL-C, TG, Apo-A1, Apo-B, Lp(a) and FB in this setting. Subjects with TC levels between 7.0 mmol/l and 9.9 mmol/l were assigned at random to treatment with MPPG (3 x 150 mg daily) or placebo. Clinical chemistry parameters were assessed at the start of the intervention and after 1, 3, 6, 9 and 12 months. Efficacy of MPPG was measured after 3 months. Long-term effect in general practice (clinical effectiveness) was measured by combining the results after 3, 6, 9 and 12 months. It was necessary to process the data in this way because of poor medication compliance. No statistically significant differences in the efficacy and clinical effectiveness of the medication in lowering TC were found between the MPPG group and the placebo group. The same was demonstrated for the other clinical chemistry values, except for LDL-C (effectiveness, p=0.04). It was concluded that the efficacy and clinical effectiveness of MPPG are too poor to justify its application as a lipid-lowering drug in general practice.

What we have learned from the Mierlo Project with regard to primary prevention of CVD in general practice is discussed in **Chapter 9**. A general screening program in a primary care setting, like that performed

in the Mierlo Project, is not an appropriate method for finding subjects at high CVD risk. It is questionable if such a program is cost-effective in view of the huge effort it requires. An alternative would be to start by identifying smokers in the more advanced age groups, who are easy and cheap to detect and are at high relative CVD risk.

The two cross-sectional studies confirmed that smoking is a major risk factor for CVD, aggravating clinical chemistry factors particularly in hypercholesterolemic subjects. The subpopulation data from the first screening had also shown that the percentage of subjects at CVD risk was higher among smokers than among non-smokers, viz. 18 and 6%, respectively, for men and 4 and 0%, respectively, for women.

Although the two prospective studies found a rather small number of incident cases of MI and first stroke, these two studies have shown that vital exhaustion merits greater attention and investigation as part of the primary prevention of CVD. In the current Dutch situation, vital exhaustion is an underestimated risk indicator, whose incorporation in future preventive studies is recommended.

This is even more important if we take into account the high percentage of Dutch adults who report being fatigued, as has recently been established in a national study. Fatigue has been established as a serious threat to health in the general Dutch population, embedded in a much broader range of health problems. The Mierlo Project shows that this also applies to the main group of illnesses in the Netherlands, CVD. Besides its predictive value, this makes vital exhaustion an important factor in general practice in terms of treatment as well. This may also be an incentive for the NHG to start research in this field, with the ultimate aim of drawing up guidelines for GPs on how to deal with fatigue, especially in relation to CVD, which, of all diseases, carries the highest morbidity and mortality rates.

This chapter also discusses the role of the GP in primary prevention. Nationally and internationally, much effort is being spent on this theme and a major role is often assigned to the GP. However, the GP is not properly trained for many activities which are major aspects of primary prevention, ranging from organizational management to psychological counseling. Primary prevention also involves influencing smoking habits and other lifestyle factors, including dietary habits and physical exercise. We recommend the introduction of experts from other disciplines, such as psychologists, dieticians and other 'health advisors'.

Finally, the main role in primary prevention should be assigned to each individual man or woman. Their willingness to maintain their cardiovascular and general health and, if applicable, to decrease their CVD risk, is critical. This is emphasized by experiences from the intervention component of the Mierlo Project. In the clinical trial, compliance with lipid-lowering medication was found to be poor, even though the intervention only involved taking three tablets daily without costs, which is much easier than, for example, smoking cessation or improving one's lifestyle. Treatment of a condition without symptoms remains difficult, as has been confirmed by other studies. This underlines that each individual person must be aware of the relevance of primary prevention and be willing to act accordingly in order to achieve a measurable effect.

Samenvatting

Dit proefschrift beschrijft het Mierlo Project. In dit project zijn risicofactoren voor hart- en vaatziekten (HVZ) bestudeerd in een eerstelijnspopulatie. Hun verbanden, klinische uitkomsten en respons op interventie komen respectievelijk aan de orde.

Alvorens aan primaire preventie te kunnen doen, is het noodzakelijk kennis te hebben van risicofactoren. De Framinghamstudie, gestart in 1948, heeft veel bijgedragen aan ons begrip van risicofactoren voor HVZ. Algemeen erkende risicoindicatoren en -factoren zijn leeftijd, mannelijk geslacht, positieve familieanamnese, roken, hoge bloeddruk, diabetes mellitus (DM), een te hoog cholesterolgehalte (TC) en verstoorde aanverwante lipidenparameters en een te hoog fibrinogeengehalte (FB). Nieuwe risicoindicatoren worden nog steeds gevonden, waaronder nog niet zo lang geleden vitale uitputting.

In Nederland zijn de identificatie en het adviseren van personen met een verhoogd risico van HVZ onderdeel van de dagelijkse praktijk van de huisarts. De laatste jaren is men begonnen met het ontwikkelen van werkbare modellen om de preventieve zorgverlening in de huisartsenpraktijk voor wat betreft HVZ te optimaliseren. Dit resulteerde in 1998 in de start van het project 'Preventie: maatwerk', een initiatief van het Nederlands Huisartsen Genootschap (NHG) en de Landelijke Huisartsen Vereniging (LHV) en van 'Hartslag Limburg', een project binnen het kader het programma 'Towards Unity for Health' van de Wereld Gezondheids-organisatie (WHO). Huisartsen spelen in beide projecten een prominente rol.

Het Mierlo Project is gewijd aan verschillende aspecten van het risico van HVZ in een huisartsensetting. De doelstellingen van het project zijn in **hoofdstuk 1** van dit proefschrift als volgt geformuleerd:

1. het vaststellen van de invloed van roken op low density lipoproteïne-cholesterol (LDL-C), high density lipoproteïne-cholesterol (HDL-C), triglyceriden (TG) en FB, in een populatie van personen met een verhoogd TC;
2. het vaststellen of vitale uitputting een risicofactor is voor een myocardinfarct (MI) of eerste beroerte (CVA);
3. het vaststellen of het geneesmiddel magnesium-pyridoxal-5'-fosfaat-glutamaat (MPPG) de bloedwaarden van TC, LDL-C, HDL-C, TG, apolipoproteïne-A1 (Apo-A1), apolipoproteïne-B100 (Apo-B), lipoprotein a [Lp(a)] en FB beïnvloedt.

Hoofdstuk 1 beschrijft in het kort wat bekend is over risicofactoren,

vooral in het licht van primaire preventie in de huisartsenpraktijk. Ook zijn in dit hoofdstuk de doelstellingen van het Mierlo Project geformuleerd. In hoofdstuk 2 worden het design en de setting van het Mierlo Project beschreven, terwijl in hoofdstuk 3 wordt ingegaan op aspecten die de studiepopulatie betreffen. In de hoofdstukken 4 tot en met 8 worden de vijf studies beschreven die als onderdelen van het Mierlo Project zijn uitgevoerd: twee cross-sectionele studies (hoofdstukken 4 en 5), waarin de onderlinge verbanden tussen roken en een aantal klinisch-chemische bloedwaarden in personen met een hypercholesterolemie werden onderzocht; twee prospectieve studies (hoofdstukken 6 en 7), waarin werd nagegaan of vitale uitputting een risicofactor is voor MI en CVA, en een interventiestudie (hoofdstuk 8), waarin de werking van MPPG op klinisch-chemische bloedwaarden werd onderzocht. Hoofdstuk 9 beschrijft wat de bevindingen van het Mierlo Project kunnen betekenen voor de primaire preventie van HVZ in de Nederlandse huisartsenpraktijk.

Het project werd uitgevoerd in het dorp Mierlo, zoals beschreven in **hoofdstuk 2**. Het betreft een doorsnee, maar niet representatieve West-Europese bevolking. Mierlo is een dorp met ongeveer 10.000 inwoners, gelegen 15 km ten zuidoosten van Eindhoven. In dit dorp werken de vijf huisartsen samen in een gezondheidscentrum. Voor het Mierlo Project was een speciaal pand ingericht, gescheiden van het gezondheidscentrum, waar de selectie-procedure plaatsvond en van waaruit het project werd gemanaged. In dit selectiecentrum waren een ervaren praktijk-research-assistente en een speciaal voor het project opgeleide onderzoeksasisstente verantwoordelijk voor de logistiek (de mailings, het maken van de afspraken, transport van de bloedmonsters), de meting van de bloeddruk en van lengte en gewicht van de proefpersonen. Zij prikten het bloed, ook ten behoeve van de interventiestudie, en vroegen de proefpersonen naar hun leefgewoonten, inclusief hun rookgedrag.

De tabel laat de belangrijkste stappen zien van het Mierlo Project, alsmede de ondernomen acties en de aantallen proefpersonen in de opeenvolgende stappen. De eerste stap van de selectieprocedure betrof het invoeren van 5894 proefpersonen in een database. Deze personen waren in de leeftijd van 26 tot en met 66 jaar en getraceerd in het bevolkingsregister van de gemeente. De personen ontvingen een brief samen met een eenvoudige vragenlijst over bij hen mogelijk aanwezige risicofactoren voor HVZ:

1. Heeft u last van hart- of vaatziekten?
2. Heeft of had uw vader, moeder, zus, broer last van hart- en vaatziekten of verhoogd cholesterol?
3. Heeft u suikerziekte?
4. Heeft u hoge bloeddruk?
5. Is uw gewicht in kg meer dan uw lengte in cm minus 100?
6. Rookt u meer dan 5 sigaretten per dag?

Wanneer één of meer vragen van de teruggestuurde vragenlijst met 'ja' was beantwoord, werd de respondent uitgenodigd voor het eerste bezoek in het selectiecentrum. Dit bestond uit metingen van het TC, de diastolische bloeddruk (DBD) en systolische bloeddruk (SBD), lengte en gewicht. Personen in de leeftijd tussen de 41 en 66 jaar werd het 'Maastricht Interview on Vital Exhaustion' (MIVE) afgenomen. Dit interview bestaat uit 23 vragen over ongewone vermoeidheid, verlies van energie, toegenomen prikkelbaarheid en gevoelens van demoralisatie (zie appendix). Alle proefpersonen met een TC ≥ 7.0 mmol/l werden voor een tweede en derde bezoek uitgenodigd. Tijdens deze bezoeken was de procedure bijna identiek aan het eerste bezoek (behalve het afnemen van

Tabel. Stroomdiagram van het Mierlo Project. Op de diverse momenten vielen proefpersonen om verschillende redenen uit (weigering van verdere deelname, verhuizing, sterfte en exclusie door de onderzoekers).

Onderdeel	actie	aantal	(%)	
Selectie	Ingeschreven, vragenlijst gestuurd	5894	(100)	
	Terugontvangen vragenlijsten	5368	(91)	
	Alle 6 vragen 'nee'	973	(17)	
	Tenminste 1 vraag 'ja'	4395	(75)	
	Eerste screening	4090	(69)	
	MIVE-subpopulatie: 41-66 years	2433	(41)	Studies, beschreven in hoofdstukken 6 en 7
	Tweede screening	506	(9)	
	Derde screening	492	(8)	Studies, beschreven in hoofdstukken 4 en 5
Interventie	Klinische studie met MPPG	202	(3)	Studie, beschreven in hoofdstuk 8
Vaststelling eindpunten	Gevallen met MI en/of eerste CVA	2433	(41)	Studies, beschreven in hoofdstukken 6 en 7

MIVE-subpopulatie: personen die de Maastricht Interview Vital Exhaustion ondergingen
MPPG: magnesium-pyridoxal-5'-fosfaat-glutamaat MI: myocardinfarct; CVA: beroerte

de MIVE). Tijdens het derde bezoek werd ook bloed geprikt voor het vaststellen van de bloedwaarden van LDL-C, HDL-C, TG, Apo-A1, Apo-B, Lp(a) en FB.

De interventiestudie betrof een vergelijking van het als lipidenverlagende middel te boek staande MPPG met placebo. Van de 492 personen met een TC ≥ 7.0 mmol/l tijdens het derde bezoek, namen uiteindelijk 202 personen mee aan deze klinische studie. Bij 112 van de 492 proefpersonen werd een gemiddelde TC (van de drie achtereenvolgende metingen) gevonden lager dan 7.0 mmol/l, op grond waarvan ze geëxcludeerd werden. Andere redenen van exclusie waren het niet voldoen aan de inclusiecriteria (n=116) en het weigeren om verder deel te nemen (n=54). De interventie duurde één jaar, waarin zes bezoeken plaatsvonden bij de huisarts. De procedure van deze vervolgbezoeken bij de huisarts was ongeveer gelijk aan het tweede en derde bezoek in het selectiecentrum.

De eindpunten voor vitale uitputting werden ongeveer vijftig maanden na het eerste bezoek in het selectiecentrum vastgesteld. De huisartsenkaarten werden gebruikt om vast te stellen of een persoon in de MIVE-subpopulatie een MI of een eerste CVA had doorstaan.

In **hoofdstuk 3** worden de studiepopulatie en de verschillende subpopulaties meer in detail beschreven. Er was geen groot verschil wat betreft het voorkomen van hoge bloeddruk, DM, overgewicht en rookgewoonten tussen de studiepopulatie en de Nederlandse bevolking.

Van het grootste deel van de subpopulatie tijdens de eerste screening (n=3514) werd met behulp van de Coronary Risk Chart (CRC) het risico van coronaire hartziekten (CHZ) geschat. De risicoschatting van een individu met deze kaart is eenvoudig en gebaseerd op de variabelen leeftijd, geslacht, rookgewoonten, TC- en SBD-waarden. Gezonde personen met een hoog risico werden gedefinieerd als zij bij wie het risico om binnen tien jaar CHZ te krijgen, groter is dan 20%. In onze subpopulatie waren dat vooral rokers (66%), waarvan 77% mannen. Werd de CRC toegepast op de MIVE-subpopulatie, dan bleek dat 5% van de uitgeputte proefpersonen een hoog risico hadden, voornamelijk vrouwen (9%, versus 5% mannen), gelijkelijk verdeeld over rokers en niet-rokers.

De twee cross-sectionele studies werden uitgevoerd bij de hypercholesterolemische proefpersonen van het derde bezoek. Deze subpopulatie werd onderverdeeld in vier subgroepen, op basis van leeftijd en geslacht (mannen < 50 jaar, mannen ≥ 50 jaar, vrouwen < 50jaar, vrouwen

≥ 50 jaar). Het cohort bestond uit 492 personen met een aanvankelijke TC-waarde ≥ 7.0 mmol/l.

Hoofdstuk 4 beschrijft de relaties tussen rookgewoonten enerzijds en LDL-C, HDL-C en TG anderzijds. De relatieve verschillen tussen rokers en niet-rokers wat betreft de gemiddelde waarden van TC, LDL-C, HDL-C en TG waren respectievelijk 2,2%, 5,5%, -8,1% en 13,7%. In het gehele cohort, bij zowel mannen als vrouwen, bleek leeftijd de gemiddelde waarden niet significant te beïnvloeden, behalve voor TC en TG in vrouwelijke rokers, welke significant hoger waren bij vrouwen ouder dan vijftig dan bij jongere vrouwen. Geconcludeerd werd dat roken niet alleen een op zichzelf staande risicofactor voor HVZ is, maar dat het de kans op HVZ verder doet toenemen in een hypercholesterolemische populatie, door zijn ongunstige werking op de waarden van LDL-C, HDL-C en TG. Stoppen met roken lijkt zelfs effectiever in hypercholesterolemische mannen en vrouwen, ongeacht leeftijd, om het risico van HVZ te verlagen dan in een normocholesterolemische groep.

In **hoofdstuk 5** wordt het verband tussen roken en FB beschreven. De gemiddelde FB-waarden van rokers en niet-rokers in de vier subpopulaties (mannen < 50 jaar, mannen ≥ 50 jaar, vrouwen < 50jaar, vrouwen ≥ 50 jaar) volgden de gemiddelde TC-waarden. Drie subpopulaties lieten verschillen in gemiddelde TC- en FB-waarden zien tussen rokers en niet-rokers: in mannen < 50 jaar van respectievelijk 2,4% (niet significant) en 15,8%, in mannen ≥ 50 jaar van 4,6 en 18,3% en in vrouwen ≥ 50 jaar van 3,2 en 8,8%. Bij de jongere vrouwen (< 50 jaar) werden geen verschillen gevonden tussen rokers en niet-rokers. Rokers in deze laatste groep hadden opvallende lage FB-waarden. Hetzelfde werd gezien voor de TG-waarde in de andere cross-sectionele studie. Deze was 12% lager in de groep jongere vrouwelijke rokers dan in de groep oudere vrouwelijke rokers. Dit verschil was echter niet significant. Voor beide lage waarden kon geen verklaring worden gevonden. Geconcludeerd werd dat het effect van roken op FB veel sterker is dan op TC. Roken is mogelijk ook een risicofactor voor HVZ door zijn effect op FB.

Het is bekend dat vermoeidheid frequent voorkomt na een MI en een CVA. Bij het MI is deze klacht vaak al vóór het incident aanwezig. Deze observatie bracht ons ertoe om twee prospectieve studies uit te voeren naar de voorspellende waarde van vitale uitputting voor MI en een eerste CVA. Vitale uitputting wordt gedefinieerd als een staat van ongewone ver-

moeidheid, verlies van energie, toegenomen prikkelbaarheid en gevoelens van demoralisatie.

De Maastricht Interview on Vital Exhaustion (MIVE; zie appendix) werd gebruikt om de mate van vitale uitputting te meten in een subpopulatie (n=2433) van personen van 41 tot en met 66 jaar, geselecteerd tijdens de eerste screening. Andere risicofactoren voor HVZ die in deze studies werden betrokken, waren leeftijd, geslacht, SBD en DBD, TC, Quetelet index (QI), rookgewoonten, reeds bestaande HVZ en DM. De eindpunten MI (fatale en niet-fatale MI) en eerste CVA werden na mediaan 50,8 maanden bepaald.

In **hoofdstuk 6** wordt ingegaan op de voorspellende waarde van vitale uitputting voor MI. Op het univariate niveau bleek vitale uitputting het risico van MI te verdubbelen (RR=2,54; 95% BI 0,97-6,64). Geslacht bleek een confounder te zijn. Vrouwen hadden hogere scores voor uitputting dan mannen en een lagere incidentie van MI. Werd er gecontroleerd voor geslacht, leeftijd, SB, TC, rookgewoonten, reeds bestaande HVZ en DM, dan bleek dat vitale uitputting de kans op een MI bijna verdrievoudigt (RR=2,91; 95% BI 1,07-7,92). Van de andere determinanten bleek alleen reeds bestaande HVZ hoger te scoren (RR=3,51; 95% BI 1,57-7,86). De conclusie was dat het bepalen van vitale uitputting een bijdrage levert aan de identificatie van personen met een verhoogd risico van MI in de huisartsenpraktijk.

Hoofdstuk 7 beschrijft een studie waarin is onderzocht of vitale uitputting een precursor is voor een eerste CVA, gecontroleerd voor andere risicofactoren van HVZ. Vitale uitputting deed het risico van een CVA toenemen met 13% per punt op de MIVE (P=0,003). Dit getal bleef statistisch significant en veranderde nauwelijks wanneer gecorrigeerd werd voor andere risicofactoren. Geconcludeerd werd dat een staat van uitputting één van de risicoindicatoren is voor een eerste CVA. Dit betekent dat vermoeidheid, zoals die zo vaak gezien wordt na een CVA, door veel patiënten al wordt ervaren voordat de CVA heeft plaatsgevonden.

De klinische studie met MPPG wordt in **hoofdstuk 8** beschreven. Deze gerandomiseerde, dubbelblinde, placebogecontroleerde klinische studie duurde twaalf maanden en werd uitgevoerd in de huisartsenpraktijk. Het doel was om het effect van MPPG op TC, LDL-C, HDL-C, TG, Apo-A1, Apo-B, lp(a) en FB vast te stellen in een dagelijkse setting. Proefpersonen met TC-waarden tussen 7,0 mmol/l en 9,9 mmol/l werden willekeurig

verdeeld over de groepen die MPPG kregen (3 x daags 150 mg) of placebo. De klinisch-chemische waarden werden bij het begin van de interventie en na één, drie, zes, negen en twaalf maanden bepaald. Het effect van MPPG werd na drie maanden vastgesteld. Het lange termijneffect in de huisartsenpraktijk (klinische effectiviteit) werd vastgesteld door de waarden, gemeten na drie, zes, negen en twaalf maanden, samen te nemen. Het was nodig om de data op deze manier te analyseren omdat de medicatietrouw te wensen overliet. Zowel voor het effect als voor de klinische effectiviteit van MPPG op TC werden geen statistisch significante verschillen gevonden tussen de MPPG- en de placebogroep. Hetzelfde resultaat gold voor de andere klinisch-chemische waarden, behalve voor LDL-C (effectiviteit, p=0,04). De conclusie was dat het effect en de klinische effectiviteit van MPPG te mager zijn om verdere toepassing van dit middel als lipidenverlager in de huisartsenpraktijk te rechtvaardigen.

In **hoofdstuk 9** wordt beschreven wat we van het Mierlo Project hebben geleerd ten aanzien van primaire preventie in de huisartsenpraktijk. Een algemeen screeningsprogramma in een eerstelijnssetting, zoals uitgevoerd in het Mierlo Project, is niet geschikt om personen met een verhoogd risico van HVZ op te sporen. Gezien de grote krachtsinspanning die het vergt om een programma als dit uit te voeren, is het zeer de vraag of de inspanning kosteneffectief is. Misschien is het een goed alternatief om te beginnen met het identificeren van rokers in de hogere leeftijdsgroepen. Opsporing van deze personen is gemakkelijk en goedkoop. Bovendien hebben zij een hoger risico van het krijgen van een HVZ.

De twee cross-sectionele studies bevestigden dat roken een belangrijke risicofactor is voor HVZ. Roken bleek de klinisch-chemische factoren in personen met een te hoog cholesterol te verergeren. Ook uit de gegevens van de subpopulatie tijdens de eerste screening was al gebleken dat het percentage personen met een HVZ-risico hoger is bij de rokers dan bij de niet-rokers, respectievelijk 18 en 6% bij de mannen en 4 en 0% bij de vrouwen.

Hoewel in de twee prospectieve studies een tamelijk lage incidentie van MI en eerste CVA werden gevonden, lieten deze twee studies zien dat vitale uitputting grotere aandacht verdient en beter onderzocht dient te worden als onderdeel van primaire preventie van HVZ. In de huidige Nederlandse situatie is vitale uitputting een onderschatte risico-indicator. Het verdient aanbeveling om deze factor in toekomstige preventieve onderzoeken mee te nemen. Deze aanbeveling wordt onderstreept door

de hoge prevalentie van moeheid in de Nederlandse volwassenen bevolking, zoals onlangs in de *Second national study into diseases and actions in general practice* werd vastgesteld. Vermoeidheid is aangemerkt als een serieuze bedreiging voor de gezondheid van de gehele Nederlandse bevolking. Het Mierlo Project laat het verband zien tussen uitputting enerzijds en HVZ anderzijds, de groep ziekten in Nederland met de hoogste morbiditeit en mortaliteit. Aandacht voor de relatie tussen vermoeidheid en HVZ in de huisartsenpraktijk is daarom een aspect dat niet uit het oog mag worden verloren. Misschien ook een aansporing voor het NHG om onderzoek hiernaar te initiëren en de resultaten daarvan op te nemen in de NHG-standaarden.

Hoofdstuk 9 gaat ook in op de rol van de huisarts ten aanzien van primaire preventie. Zowel nationaal als internationaal worden op dit terrein grote inspanningen getroost. Dikwijls wordt aan de huisarts een belangrijke rol toegekend. De huisarts is voor het doen van primaire preventie echter niet goed opgeleid, zowel wat betreft het management als de psychologische begeleiding van de patiënt. Primaire preventie behelst ook interveniëren op rookgedrag en andere leefgewoonten, zoals ongezonde voedingsgewoonten en gebrek aan lichaamsbeweging. Wij bevelen aan om deskundigen van andere disciplines, zoals psychologen, diëtisten en andere gezondheidsadviseurs, hierin te betrekken.

Ten slotte, in geval van primaire preventie is de hoofdrol weggelegd voor het individu zelf. Zijn bereidheid om iets aan zijn gezondheid te doen is cruciaal, zeker waar het gaat om zijn risico van het krijgen van HVZ. Deze stelling wordt onder andere bevestigd door de ervaringen met de interventiestudie van het Mierlo Project. In dit onderzoek bleek dat de therapietrouw met het op cholesterolverlaging geteste middel laag was, ondanks het feit dat de persoon slechts drie tabletten per dag hoefde te slikken, tabletten, die kosteloos werden verstrekt. Het nemen van tabletten is veel gemakkelijker dan bijvoorbeeld stoppen met roken of veranderen van leefgewoonten. Bovendien blijft het moeilijk een conditie zonder voor de patiënt voelbare symptomen te behandelen, hetgeen ook uit andere studies naar voren komt.

Cruciaal is dat het individu ervan doordrongen is dat primaire preventie voor zijn gezondheid belangrijk is en dat hij hier actief iets aan dient te doen indien hij een meetbaar effect wil bewerkstelligen.

Appendix

Maastricht Interview Vital Exhaustion (MIVE)

1. Do you often feel tired?
   If so, for how long have you been feeling tired?
2. Have you felt listless lately?
   If so, for how long have you been feeling listless?
3. Do you feel weak all over or without energy?
   If so, for how long have you been feeling weak?
4. Have you been irritated more easily lately than before?
   If so, when did this start?
5. Do you feel dejected?
   What makes you feel that way?
6. Do you sometimes feel as if your body is like a battery that is losing it power?
7. Do you have the feeling that you have not been accomplishing much lately or that you are less capable of accomplishing things?
8. Do you ever wake up with a feeling of exhaustion or fatigue?
9. Do you wake up repeatedly during the night?
   If so, do you consider this as a problem?
10. Do you have the feeling that your cannot cope with everyday problems as well as you used to?
11. Do you feel you want to give up trying?
12. Have little things irritated you more lately than they used to?
13. Do you blow up more easily than before?
14. Do you have the feeling these days that you just do not have what is takes anymore?
15. Have you noticed a decrease in your sexual appetite or a decrease in the desire to make love?
16. Has it become harder lately to solve a mental task or problem which requires much concentration?
17. Do you have increasing difficulty in concentrating on a single subject for long?
18. Do you shrink from your regular work as if it were a mountain to climb?
19. Do you believe that you have come to a 'dead end'?
20. Do you sometimes cry or feel like crying?
21. Do you feel defeated or disillusioned?
22. Have you experienced a feeling of hopelessness recently?
23. Would you want to be dead at times?

Score MIVE: 1 question = 1 point

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Van het thuisfront
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Mijn zus Kitty †
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CURRICULUM VITAE

Gert Schuitemaker was born in Veendam, the Netherlands, on August 2nd, 1952. After graduating from secondary school (Gymnasium), he started studying pharmacy at the University of Leiden in 1971. In 1977, he spent six months at the University of Montpellier, France, where he initiated a study into the attitude of French pharmacy students towards their future profession, and their viewpoints with respect to the mutual recognition of pharmacists' diplomas in the EU. This study was later extended to cover pharmacy students in Leiden (Netherlands), Cardiff (United Kingdom) and Frankfurt (Germany), thus becoming his masters project, completing the scientific training component of his Leiden pharmacy studies in 1979. In the same year, he continued his studies at the University of Amsterdam to complete his professional education. He received his pharmacist's degree in 1984.

In the meantime, he had developed an interest in aspects of nutrition. In 1983, he established the Ortho Institute, a foundation whose purpose was to inform about nutrition and health. He is editor-in-chief of the Dutch journal Ortho. He is the former president and founder of the Maatschappij ter Bevordering van de Orthomoleculaire Geneeskunde (MBOG; Association for the Advancement of Orthomolecular Medicine) and since 1999 he has been the president of the International Society for Orthomolecular Medicine (ISOM, based in Toronto, Canada).

In 1993 he initiated the Mierlo Project, which was scientifically supervised by the University of Maastricht departments of General Practice and Medical, Clinical and Experimental Psychology. This project has resulted in the present thesis.