RANDOMISED CONTROLLED TRIAL OF SCREENING FOR TYPE 2 DIABETES MELLITUS IN OBESE SUBJECTS

Final Report Phase 1

Erasmus MC Rotterdam: Dr. SJ Otto, B Klijs, Prof. Dr. JDF Habbema, Dr. HJ de Koning
Julius Centrum - UMC Utrecht: Prof. Dr. Y van der Graaf
EMGO institute - Vumc: Prof. Dr. RJ Heine

March 2008

TABLE OF CONTENTS

1. INTRODUCTION

Diabetes is an important public health problem. It is estimated that about half a million Dutch men and women have this condition, and 30,000 to 50,000 new patients are diagnosed each year. The risk of serious complications is high: people with diabetes are two to four times more likely to die of cardiovascular disease. The number of new cases will increase over the coming years as the population ages. Prevalence is also set to increase as a result of falling levels of physical activity and the rise in (severe) obesity in the population. Various randomised treatment trials have shown that correcting glucose values and treating other risk factors that may be present can be highly beneficial to health. It has also been found that glucose values can be elevated for many years before diabetes is diagnosed, without developing any clear complaints and/or symptoms. Trying to establish a systematic approach so that diabetes can be detected earlier is therefore highly opportune. However, no studies have so far shown a clear link between systematic screening and a reduction in complications and death following early detection and treatment. Opportunistic screening via the GP would appear to be a difficult route to take because of the lack of up-to-date information on risk factors in GPs' records by which at-risk groups could be identified. Another drawback to demonstrating health benefits through opportunistic screening is the absence of a control group. We therefore need to conduct a population-based RCT in a high-risk group.

2. AIMS AND QUESTIONS

The aim of this study is to ascertain whether systematic screening for type 2 diabetes in a high-risk group (people with abdominal obesity) can reduce cardiovascular morbidity and mortality by at least 25%. The individuals eligible for the study are men and women aged from 40 to 74 with waist sizes of >=94 cm (men) and >= 80 cm (women). These relatively generous cut-off points (action level 1) were used so that elderly people and individuals of Asian descent can be included. In view of the scale of the project and the associated costs, we suggested first conducting a pilot study with specific feasibility questions among 20% of the target population and awaiting the results. Specific expectations/requirements have already been set down in the application (Subsidy application form no. 3082, 2005) which give an insight into conditions for a possible successful follow-up of the large-scale efficacy study:

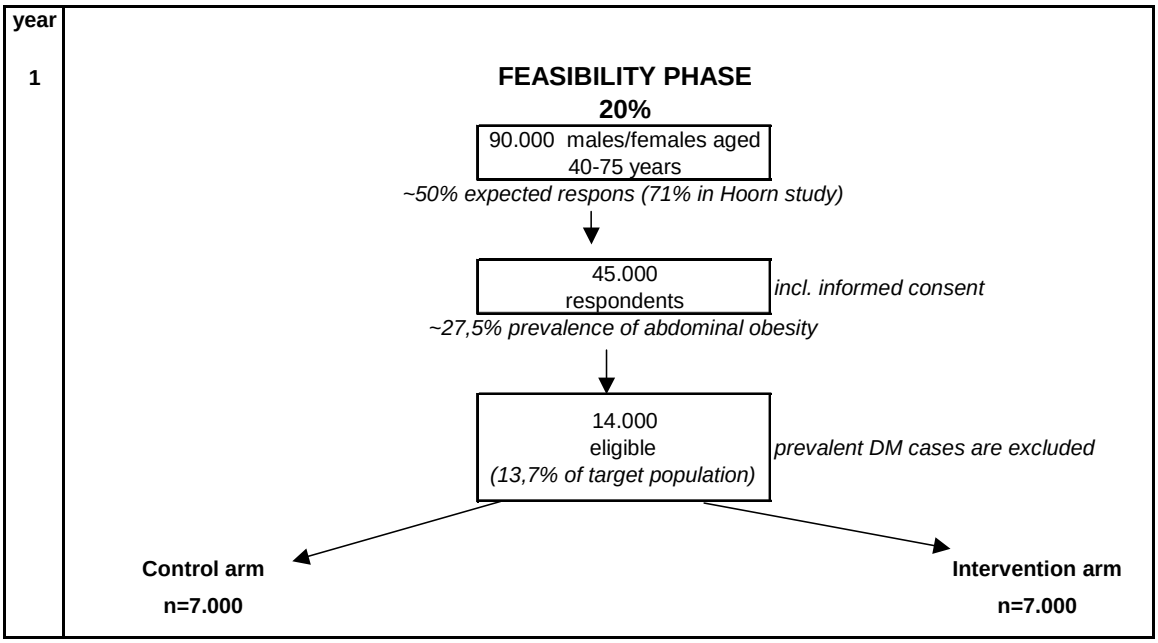
1. mailing a tape measure as the first risk test to all people aged between 40 and 75 produces a sufficiently large high-risk study population: we predict that 13.7% of the individuals contacted in this way will both fall into the high-risk group and be willing to undergo randomisation.
2. the "high risk selection test", in which the individual measures his or her own waist size, is a sufficiently valid method: a sub-group will be re-measured by an expert in order to investigate the accuracy of the data.
3. after individuals are assigned at random to the study arm (invitation to screening), a sufficient number of people would attend appointments to have their glucose and lipid levels measured.
4. a considerable proportion of the individuals who are screened would be found to have positive results that had not previously been diagnosed. They could then be referred to their GP for further diagnosis and treatment.

The following essential parameters have been addressed in order to test these expectations in the pilot study:

a. The feasibility of mailings and recruiting the high-risk group by mail; determining whether reporting waist size measured by the individual concerned is feasible for selecting a high-risk group.
b. Response to mailings: the proportion of high-risk individuals among the respondents, and the proportion of these who consent to randomisation/participation.
c. Which method of sending out mailings produces the highest response among people who are at high risk, and how much does each method cost?

d. The socio-demographic properties (including ethnic origin) of respondents.
e. The percentage of men and women in the screening group who are invited for screening and who actually undergo screening, and the number of new cases of diabetes discovered among these individuals.
f. Contamination in the control group (the percentage of people in this group who are still having their fasting glucose levels measured via their GP).
g. Costs of also measuring blood pressure.
h. Cooperation with GPs, and GP workloads, when individuals with impaired fasting glucose levels are referred to them.

Figure 1. Flowchart showing the original design of the pilot study.



3. METHODS AND ACTIVITIES

3.1 Choice of pilot regions and name and address details

The pilot phase of the study was initially intended to be carried out in the towns of Dordrecht and Zwijndrecht. This choice was taken mainly because of the broad socio-economic (SE) distribution of the inhabitants of these towns (based on data from Statistics Netherlands). These towns are also in the territory of the local health authority [GGD Zuid-Holland Zuid], with which we already had good relations. After contacting GPs we found out that GPs in Zwijndrecht were planning to carry out a project to record risk factors for cardiovascular disease. Part of this would include detecting undiagnosed diabetes. As this project would very probably lead to an overlap within our control group and we were unable to sort out a cooperation agreement in the short term, we decided after a few months not to carry out our project in Zwijndrecht, and opted for Capelle aan den IJssel instead, as this town has a very similar SE composition to Zwijndrecht.

We asked for the name and address information that we would need from local authority records, and the Residents' Affairs departments of the Capelle aan den IJssel and Dordrecht councils complied with the request. The data for Capelle arrived very quickly: we paid an administration fee and received the information within two weeks of requesting it (delivered on 13 June 2006). Things did not go as quickly in Dordrecht. We found out that under a local bye-law Dordrecht council charges € 0.50 per item requested. In mid-December 2005 we asked the council whether they would be prepared to supply the address details free of charge or at a much lower price. It took until well into 2006 for this problem to be resolved through the official channels. In early June it was established that the council had changed its charging system for name and address data from local authority records, and that the data needed for the pilot study could be provided at a low price (which eventually worked out at €0.09). We received the data on 5 July 2006.

3.2 Project material

- **Mailings.** We contacted the target population via mailings of the study material, comprising a letter of invitation, an information brochure and a tape measure. The letters of invitation and a declaration of consent were drafted for this purpose, and an information brochure was written. The material was written with the help of a communications specialist, Bureau Taal, to ensure that it would be understood by people with a low level of educational attainment. We also drew up a questionnaire asking about height, weight, marital status, risk factors and socio-economic status. Artex V.O.F. was in charge of the layout, printing and dispatch of the project material (including a tape measure and lifestyle information) and of processing the responses.
- **Dispatch.** In the two towns the mailings were sent out in two different ways. Half the population received the complete study material, consisting of a letter of invitation, information brochure, tape measure and declaration of consent, all sent at the same time (Method 1). The other half first received just a letter of invitation containing a brief introduction to the study, an explanation of how to measure waist size, and a tape measure. Individuals who responded and who were judged potentially eligible were then sent an accompanying letter, information brochure and declaration of consent (Method 2). The aim of this was to find out which method produced the greatest response from people at high risk, and what the costs of each method were.
- **Lifestyle information.** Generic written information about a healthy lifestyle was sent to participants in the screening group and the control group. This information was drawn up in the light of advice from the section of Determinant of health-related behaviour (*Determinanten van Gezond Gedrag*) of the department of Public Health, which has extensive experience with lifestyle research. It took account of various inputs, including recommendations issued by the Nutrition Centre, which approved the material.
- **Medical ethics committee approval.** The research proposal was approved by the medical ethics committee of Erasmus MC. The matter was first discussed at a meeting held on 13 December 2005. The committee asked a number of questions and made some comments on the protocol, the patient information and consent form and the General Assessment and Registration (ABR) form in letters sent to us dated 22

December 2005 and 22 February 2006. The committee was satisfied with our replies and finally approved the trial protocol. It is registered in the Netherlands Register of Trials under no. ISRCTN75983009.

3.3 Data collection

- **Database**. The Diabetes dataManagement System (DMS) was developed in cooperation with Artex V.O.F. to store all the data relating to participants collected during the study. Correspondence with participants, including randomisation letters and lab test results, was generated by DMS and sent out by Artex V.O.F.
- **Lab tests.** The fasting glucose levels of all participants in the screening group was measured. To get this work done in Dordrecht, the clinical chemistry laboratory of the Albert Schweitzer Hospital (Asz) in Dordrecht and the GP Laboratory Foundation (SHL) in Etten-Leur were contacted. Once Capelle had been selected as the second pilot location, we contacted the Star-MDC GP laboratory in Rotterdam to investigate options in Dordrecht and Capelle. Having examined the estimated costs (Table 1) charged by these facilities, we finally decided to use Star-MDC. Once randomisation had been completed, the first invitations for screening and blood samples at a Star-MDC site were sent to participants in Capelle (mid-October 2006) and Dordrecht (end of November 2006). The first group of participants invited were mainly those who had been approached via method 1.
- **Cooperation with GPs.** We contacted the KOEL Foundation (a body that offers training and support to GPs in Zwijndrecht), the chairman of the Dordrecht regional GPs' association and the Capelle GPs' foundation to tell GPs in the region about the project and ask for their support. We sent letters to GPs in the pilot towns in late June/early July 2006, informing them about the project and enclosing relevant project information.

Table 1. Estimated costs charged by the three GPs' laboratories in euros

	Own budget	A	B	C
Venipuncture/lab analyses	64.000,00	83.174,40	199.296,26	77.368,50
gemeente		*Dordrecht*	*Dordrecht & Capelle*	*Dordrecht & Capelle*
Extra costs for measuring blood pressure & re-measuring waist circumference			7.977,90	4.000,00
Total	64.000,00	83.174,40	207.274,16	81.368,50

4. RESULTS

The local authorities of the towns involved, Capelle aan den IJssel and Dordrecht, provided 79,166 sets of name and address details. This determined the population size for the pilot project at 15% of the intended population (instead of 20%, see Figure 1)). Twenty-four individuals could not be contacted by letter as the local authority did not provide an address for them. The results of the questions listed in section 2 are given below.

4.1 Response

4.1.1 Response to mailings

Table 2 shows the total number of respondents, the number of suitable respondents, and the number who also gave consent to take part in the study. When drafting the project proposal we expected that we would be able to include 13.7% of all people to whom we had written as members of the high-risk group. In practice we managed to randomise 10,609 high-risk people (13.4%).

Table 2. Summary of the number of respondents after each stage

	Total	Observed
Number invited	79,142	
Total number of initial respondents*	20,578	26.0%
Number of eligibles based on waist circumference criteria	*16,135*	*20.4%*
Number of eligibles †	15,174	19.2%
Gave informed consent	10,699	13.5%
Randomized:	10,609	13.4%
control arm	5,304	
screening arm	5,305	

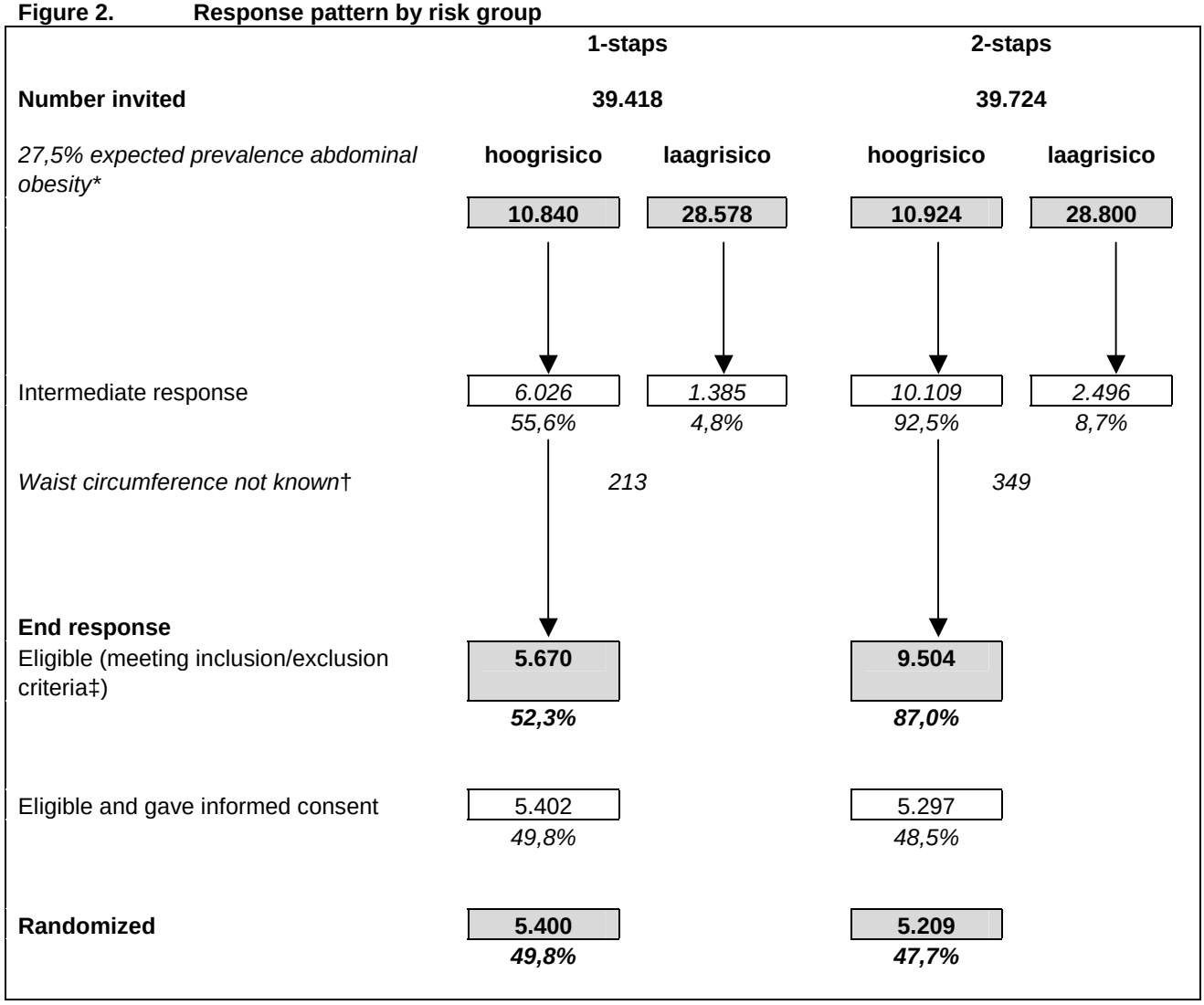
* the letter clearly explained what 'high-risk' meant and how to measure waist size (see appendix and below).
† Excluding people already diagnosed with diabetes and people who had had a CVA, TIA or MI in the preceding year.

4.1.2. Response by risk group

The mailings were sent out in two different ways in order to find out which method achieved the highest response among people at high risk. Figure 2 below shows the response to the two contact methods among those members of the target population expected to be at high risk or at low risk based on an expected prevalence of abdominal obesity of 27.5% in people aged between 40 and 74. As described in the project proposal, this percentage is based on various sources of information, including data from the MORGEN study published in *The Lancet* in 1998 (Lean et al.). 55.6% of people with abdominal obesity responded to the one-step method (declaration of consent sent out with the initial letter) compared to only 4.8% of people not expected to have abdominal obesity. In the two-step approach (declaration of consent sent out later), only 8.7%

of people who were not abdominally obese responded, compared to 92.5% of people with abdominal obesity. 48.5% of individuals in the latter group (excluding those covered by the exclusion criteria) consented to randomisation when asked whether they would do so. So if we look at the right target group, people with abdominal obesity, the initial response was around 70%, as we expected (for both methods) and the final, effective response of the high-risk group (including informed consent and excluding existing diabetic patients) was 49% (10,699 of the 21,764 people expected to have abdominal obesity). We will use method 1 in the rest of the study, as it should produce an inclusion rate of 13.7%.

Figure 2. Response pattern by risk group



* AO, abdominal obesity.

† waist size not given on the questionnaire.

‡ abdominal obesity, excluding people already diagnosed with diabetes and people who had had a CVA, TIA or MI in the preceding year.

4.2 Demographic and socio-economic characteristics of respondents

Table 3 shows the characteristics of the respondents and of the people allocated at random to the screening and control groups. The table compares the characteristics of the respondents with data from the 2005 Health Survey conducted by the Rotterdam-Rijnmond local health authority for Capelle aan den IJssel (Schouten & Kuilman, 2007) and from the 2006 Health Monitor conducted by the Zuid-Holland Zuid local health authority for all local authorities (Terpstra et al., 2006).

More than half of the respondents were women, and 77% were ex-smokers or had never smoked. Most of the respondents were married or cohabiting.

This figures follow a similar pattern to those of respondents in the two regional health surveys. This shows that based on demographic characteristics the composition of the study cohort is representative of the general population.

Table 3. Characteristics of the initial respondents and of those participating in randomisation

	Initiële respondenten N=20.578		Gerandomiseerd N=10.609		GGD RR*	GGD ZHZ†
	N	*%*	*N*	*%*	*%*	*%*
Age‡						
Median	55,6		56,6			
Range	39,5 - 75,7		39,9 - 76,1		16 – 84 jaar	≥19 jaar
Gender						
Male	9.521	46,3	4.656	43,9	46	44,1
Female	11.025	53,6	5.953	56,1	54	55,9
Missing	32	0,2				
Smoking status						
Current smoker	4.549	22,1	2.042	19,2	23,9	25
Ex-smoker/never smoker	15.857	77,1	8.523	80,3		
Missing	172	0,8	44	0,4		
Marital status						
Married, living together	16.061	78,0	8.479	79,9	65,9	76
Unmarried	1.426	6,9	671	6,3	21,3	13
Divorced	1.636	8,0	786	7,4	7,7	5
Widow/widower	1.068	5,2	530	5,0	5,0	6
Missing	387	1,9	143	1,3		

* 2005 health survey conducted by Rotterdam-Rijnmond local health authority (Capelle aan den IJssel).

† 2006 Health Monitor conducted by Zuid-Holland Zuid local health authority (all local authorities).

‡ age of people taking part in randomisation at the time of randomisation.

Table 4 shows the distribution of respondents' levels of educational attainment. 49.2% of the respondents had not pursued their studies further than lower general secondary education, and a similar percentage had gone on to higher general secondary education. These findings are comparable to data for Capelle obtained from the 2005 Health Survey conducted by the Rotterdam-Rijnmond local health authority (45%) and the 2006 Health Monitor produced by the Zuid-Holland Zuid local health authority (52%). So in general terms this study is not selective for educational level.

Table 4 Distribution by level of educational attainment

	Respondents N=20.578		Randomized N=10.609		GGD RR*	GGD ZHZ†
	N	*%*	*N*	*%*	*%*	*%*
Age range ‡	39 - 75		39 - 76		16 – 84 jaar	≥19 jaar
Highest education						
Low education§	2.023	9,9	1.011	9,5	11	13
MAVO/LBO/VMBO	8.095	39,3	4.284	40,4	34	39
HAVO/VWO/MBO	4.950	24,1	2.604	24,5		29
HBO + WO	5.173	25,1	2.602	24,5		19
Missing	337	1,6	108	1,0		

* 2005 health survey conducted by Rotterdam-Rijnmond local health authority (Capelle aan den IJssel).
† 2006 Health Monitor conducted by Zuid-Holland Zuid local health authority (all local authorities).
‡ age of people taking part in randomisation at the time of randomisation.
§ including those with no education.

Table 5 shows responses according to country of birth and socio-economic status (SES). In this report SES was based on social status. This was determined using data from the Social and Cultural Planning Office for 2006, which divides postcode areas in the Netherlands into those associated with high and low social status (ranking from 1 to 3,965). Social status is worked out on the basis of income, unemployment and levels of educational attainment in postcode areas.
Responses can only be categorised into ethnicity on the basis of the respondents' own country of birth, as information on the place of birth of the parents of individuals who were contacted was not provided by the two local authorities. The initial response among people born in a non-Western country (mainly Turkey, Surinam, the Dutch Antilles/Aruba) was 15.3% (table 5) and 27.8% among people born in the Netherlands. The lowest response was among people born in Morocco (7.8%). This pattern is repeated in the percentage distribution of the respondents. This shows that 10.2% (8,052 out of 79,142) of the people contacted were of foreign non-Western origin. Among respondents the figure was 6.0%, rising to 7.2% if the self-reported country of birth of the respondents' parents is taken into account. 'Non-Western' was defined in the terms used by Statistics Netherlands, similar to the figure shown in the Zuid-Holland Zuid local health authority health monitor (5%). The lower figure for foreigners of non-Western origin (6% compared to 10%) may indicate that this group is difficult to reach for this study, even though special attention was paid to the use of language in the study material, which was simplified by Bureau Taal.
There are also some differences between respondents and people initially contacted according to the four SES sub-groups, educational level and social status as defined by the Social and Cultural Planning Office. The

responses from individuals with high, medium to high, medium to low and low social status were 30.2%, 29.5%, 22.1% and 23.2% respectively. But if we look at the percentage distribution of the respondents we see some small differences: 53.9% of the inhabitants in the pilot towns belonged to the lowest two social status groups, defined on the basis of income, education and unemployment, but 47% of the respondents belonged to these groups.

Table 5 Response and composition of cohorts on the basis of ethnic origin and socio-economic status

	Response			**Procentuele verdeling**		
	Aangeschreven	Respondent		Aangeschreven	Respondent	Gerandomiseerd
	N=79.142	N=20.578		N=79.142	N=20.578	N=10.609
	N	N	%	%	%	%
Ethnicity						
Own birth country*						
Netherlands	66.134	18.374	27,8	83,6	89,3	91,2
Non-western country	8.052	1.233	15,3	10,2	6,0	4,8
Turkey	1.573	200	12,7	2,0	1,0	0,7
Marocco	656	51	7,8	0,8	0,2	0,1
Surinam	2.083	413	19,8	2,6	2,0	1,6
Neth.Antilles/Aruba	1.277	209	16,4	1,6	1,0	1,0
Others	2.463	360	14,6			
Western country	4.954	971	19,6	6,3	4,7	4,0
Indonesia	2.122	274	12,9	2,7	1,3	1,0
Others	2.832	697	24,6			
…and of the parents†						
Autochtone					83,4	86,3
Non-western foreigner					7,2	6,4
Western foreigner					5,5	4,4
Unknown					3,9	2,9
Social status‡						
high social status§	22.910	6.920	30,2	28,9	33,6	33,3
medium to high	13.522	3.989	29,5	17,1	19,4	18,3
medium to low	20.114	4.439	22,1	25,4	21,6	25,2
low social status	22.591	5.230	23,2	28,5	25,4	23,2

* n=2 number of people contacted whose country of birth is unknown.

† based on the respondents' own country of birth and those of their parents (self-reported data).

‡ Socio-economic status is defined according to the social status hierarchy of postcode areas (Social and Cultural Planning Office); five of the people contacted had a PO box number.

§ social status of postcodes (score in brackets):

high (58-865): 2909, 2901, 2904, 3316, 3319, 3315; medium to high (1024-1998): 3328, 2908, 3329, 2902; medium to low (2135-2839): 2907, 2906, 3311, 3312; low (3238-3841): 3318, 2903, 3313, 2905, 3314, 3317.

4.3. Waist size

Individuals were asked to measure their waist size twice. 9.4% of the respondents only reported one figure, while 81.2% reported figures in the same category. Only 0.6% gave figures that were different by two or more categories, and 1.9% did not answer the question. (The categories were: 1=70 cm, 2=71-79cm, 3=80-87, 4= 88-93 cm, 5=94-101 cm, 6= 102-110 cm, 7=111 cm). Table 6 shows the self-reported waist sizes for all respondents. The data from table 6 clearly shows that the vast majority of respondents meet the waist size inclusion criteria: 73% of men had a waist size of >= 94 cm and 84% of women had a waist size of >= 80 cm. (Note: this is three times higher than expected, and also indicates that mainly people who were at high risk felt that the letters of invitation were relevant to them). This table also shows that the percentages meeting the criterion are similar in the three 'ethnic' groups. There is a link with education. About 86% of people with a low level of educational attainment have abdominal obesity, compared to 72% of people with a high level of educational attainment. The differences are more pronounced in the case of action level 2, which indicates a larger waist size.

Table 6. Distribution of respondents' waist sizes by method, country of birth and level of educational attainment

		Male *in cm*				Female *in cm*				Action level*	
		≤ 93	94-101	≥ 102	Missing	≤ 79	80-87	≥ 88	Missing	1	2
Method 1†	(N)	856	1.191	1.437	103	529	866	2.532	96	6.026	3.969
Method 2‡	(N)	1.518	2.026	2.248	142	978	1.640	4.195	189	10.109	6.443
Total §	(N)	2.374	3.217	3.685	245	1.507	2.506	6.727	284	16.135	10.412
	(%)	24,9	33,8	38,7	2,6	13,7	22,7	61,0	2,6	78,4	50,6
Birth country (%)											
Nederland		24,3	33,8	39,4	2,5	13,8	23,2	60,6	2,5	78,9	50,8
Westerse land		30,5	36,0	30,1	3,4	16,0	23,4	58,1	2,5	74,5	45,3
Niet-westerse land		30,4	32,2	34,1	3,3	10,5	16,0	69,3	4,2	76,9	53,7
Education level (%)											
Laag opgeleid¶		16,6	28,7	49,6	5,1	5,5	14,7	76,1	3,7	85,8	65,5
MAVO/LBO/VMBO		21,7	33,2	42,6	2,6	11,1	20,8	65,9	2,2	82,4	56,7
HAVO/VWO/MBO		24,5	34,5	39,2	1,8	16,9	26,2	55,3	1,7	77,5	47,1
HBO + WO		31,5	35,7	31,3	1,6	20,2	28,6	49,6	1,6	71,9	39,4
Opleiding onbekend		18,9	25,8	31,1	24,2	12,2	10,2	49,8	27,8	58,8	42,4

* Action level 1, men >=94 cm, women >=80 cm, Action level 2, men >=102 cm, women >=88 cm.

† One-step method: Mailing: letter of invitation, brochure, questionnaire, tape measure, declaration of consent.

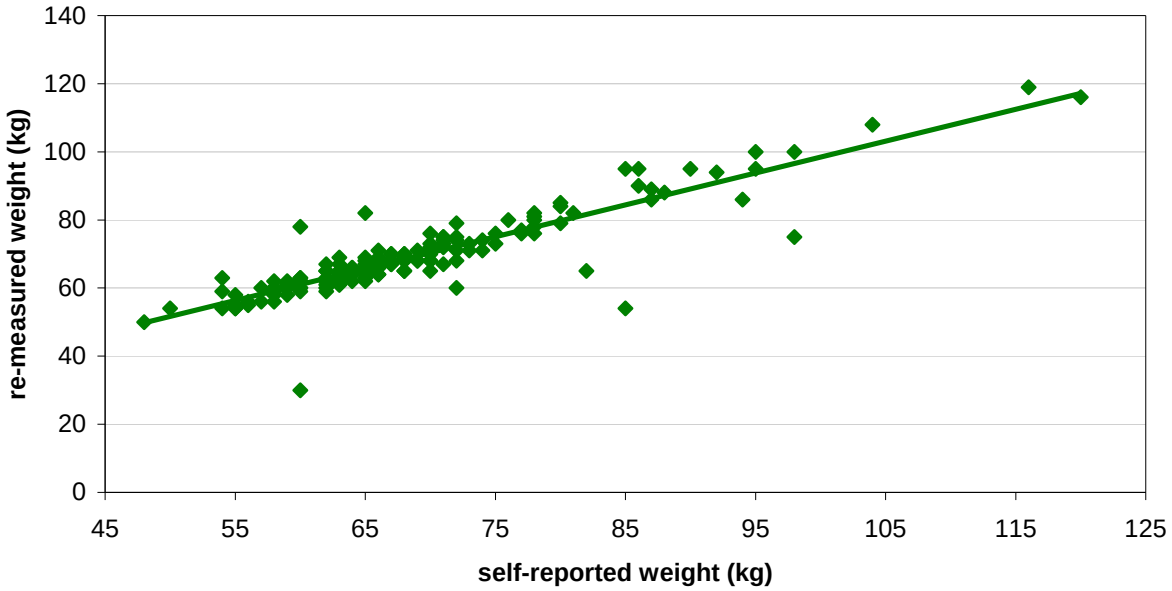
‡ Two-step method: First mailing: letter of invitation, tape measure and questionnaire, second mailing: accompanying letter, brochure, and declaration of consent for eligible respondents.

§ the figures include people who meet the exclusion criteria (see table 2)

¶ including those with no education.

A sub-sample of n=162 of those invited for screening were weighed and had their waist size measured again during the appointment at which they gave blood samples. The same sub-sample also had their blood pressure measured to investigate cardiovascular risk factor overlap. We intended to conduct these measurements on a larger sub-sample, but this was not possible in the short feasibility phase for reasons of cost and practicality. This will be done in years 2 to 4. Figure 3 shows the correlation between self-reported weight and weight as measured by STAR employees, given separately for men and women. Figure 4 shows the correlation for waist size.

Figure 3 Comparison between self-reported and measured weight, n=161 (r=0.90, p=0.000).



In the case of men, the average difference between self-reported weight and re-measured weight was -1.6 kg (possible under-reporting), excluding two people who were found on being re-measured to weigh 23 kg and 31 kg more than they had reported. In the case of women, the average difference was -0.73 kg (under-reporting by the respondent). The correlation coefficient between self-reported and re-measured results is r=0.90 (P=0.000), which is a high degree of correlation.

Waist size measurements were also found to correlate well (r=0.80 (P=0.000, figure 4)), but not entirely satisfactory in the 80-87 cm range (women). Correlations between self-measured and re-measured waist sizes are shown in figure 5 below. The correlation coefficient r=0.220 (P=0.0127) did show a weak link between the two measurements. This is probably due to inaccurate measurement of waist sizes <=87 cm.

Figure 4. Comparison between self-reported and measured waist size, n=160 (r=0.80, P=0.000).

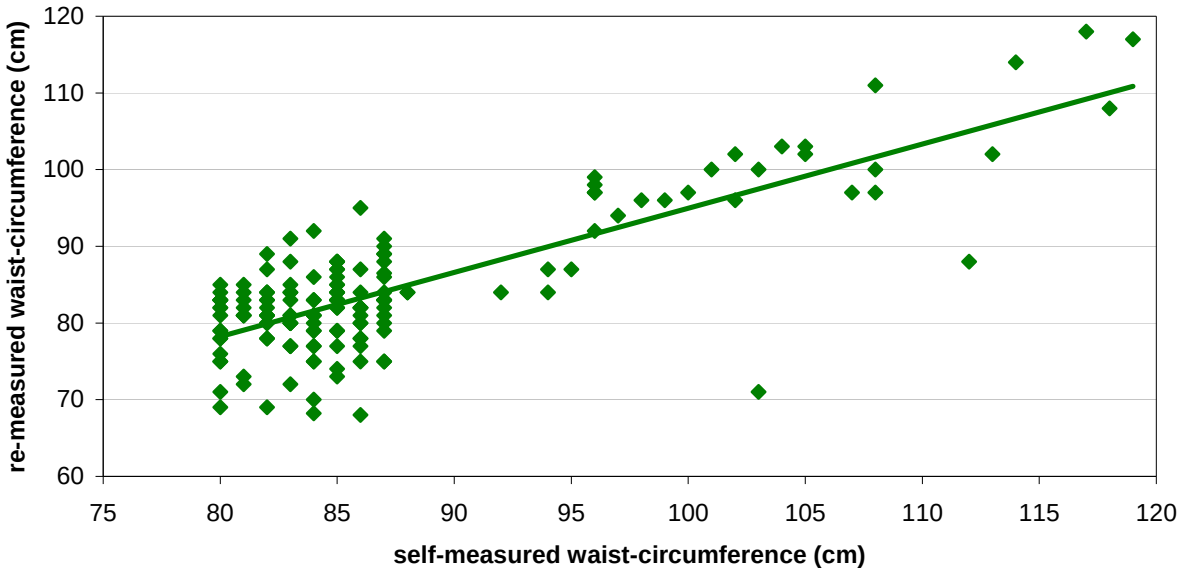
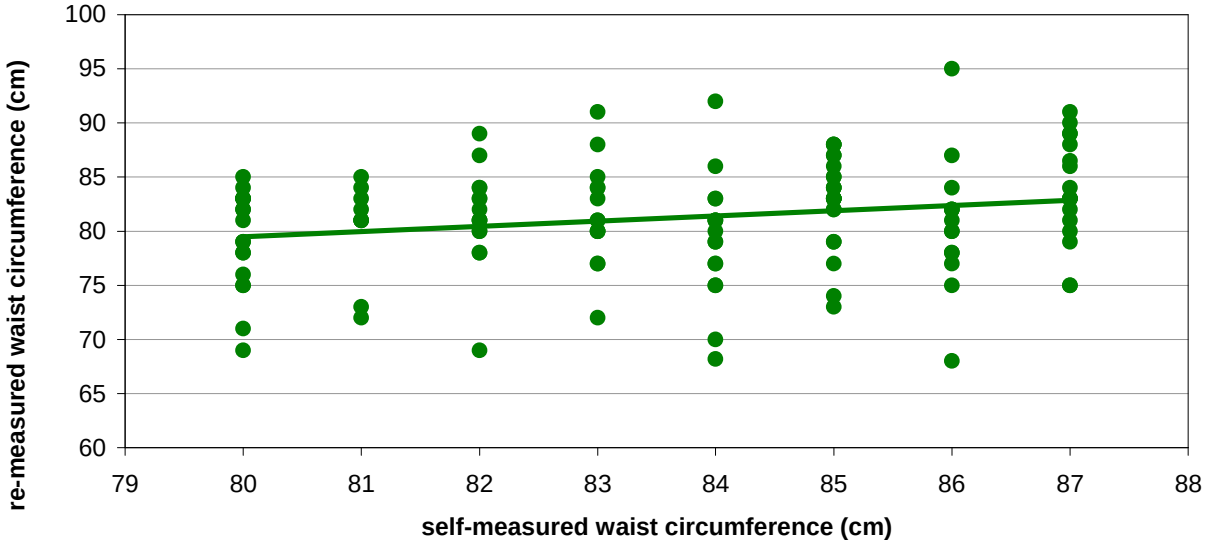


Figure 5. Comparison of self-reported waist size measurements in the 80-87 cm range by women and the re-measured results (n=127, r=0.220, P=0.0127).



Cohen's kappa was also calculated to ascertain whether self-measured waist sizes and waist sizes measured by third parties matched up for the group in action level 1 (waist size >= 94 cm for men and >= 80 cm for women). The figure is 0.64, which indicates that these two measurements correlate better than would be expected on the basis of chance.

4.4 Participation in lifestyle campaigns

As stated above, the participants were selected on the basis of their waist size (>= 80 cm for women and >=94 cm for men). Individuals who had had a CVA, TIA or MI in the past year or who were already known to be diabetic were excluded. The prevalence of diabetes (either type) among respondents was 3.7% (2.2% did not answer the question; table 7). This figure is in line with that reported in the 2006 Health Monitor conducted by Zuid-Holland Zuid local health authority (3.6%), but is lower than that given in the 2005 Health Survey conducted by Rotterdam-Rijnmond for Capelle aan den IJssel (5.3%). About 26% of the respondents and men and women who underwent randomisation have a close relative with diabetes (1.6% did not answer the question). Indian or Pakistani origin is regarded as a risk factor for diabetes; only 1.1% of the respondents in this project were of Indian or Pakistani origin.

Table 7.Diabetes risk factors and participation in lifestyle campaigns

	Respondents (N=20,578)			Randomized (N=10,609)			GGD RR*	GGD ZHZ†
	N	%		N	%		%	%
Prevalence of diabetes								
yes	756	3.7					5.3	3.6
no	19,363	94.1						
missing	459	2.2						
Participated in lifestyle campaigns‡								
yes	1.690	8.2	*9.3*§	757	7.1	*8.0*§		
no	16,453	80.0	*90.7*	8697	82.0	*92.0*		
missing	2,435	11,8		1155	10,9			
If yes, what (%):								
Measurement of waist circumference	23.4				34.2			
Diabetes risk test/questionnaire	6.1				7.0			
Measurement of blood glucose	28.9				27.6			
Measurement of blood lipids	12.3				17.0			
Others	27.4				14.2			

* 2005 health survey conducted by Rotterdam-Rijnmond local health authority (Capelle aan den IJssel).

† 2006 Health Monitor conducted by Zuid-Holland Zuid local health authority (all local authorities).

‡ question 9 in the questionnaire: "*Have you taken part in a study into diabetes or cardiovascular disease in the past six months?*".

§ percentages calculated excluding the missing data

A number of campaigns and activities relating to early detection of type 2 diabetes were launched in 2006, such as the "Kijk op Diabetes" campaign run by the Diabetes Federation. For that reason the questionnaire included a question to potential participants aimed at finding out to what extent they had already taken part in activities of this kind. Table 7 shows that only 7% of the individuals who underwent randomisation had taken part in a programme of this kind.

4.5 Blood values

The screening group was invited to give a fasting blood sample to determine plasma glucose and serum lipid values. 5,305 men and women were randomised in the screening group. Of these, n=5,302 were asked to give a blood sample (n=3 withdrew consent before receiving this request). Eventually n=4,459 (84.1%) had their blood glucose and lipid values measured (n=7 were not in a fasting state when they attended the appointment). Table 8 summarises the results.

After consultation with GPs, it was agreed that participants who did not have elevated glucose levels but were at greater risk of cardiovascular morbidity and mortality according to the Netherlands College of General Practitioners risk table (colour code yellow or red) would be advised to contact their GP. The risk was determined on the basis of whether the individual smoked, his or her age and TC/HDL ratio. Blood pressure was defined as the mean systolic blood pressure measured in a sub-sample of n=162 (median SBP 143 mmHg, mean 148.216). Table 8 shows that 5.6% of the individuals screened had impaired glucose levels and 13.0% also had impaired lipid metabolism (which according to the Netherlands College of General Practitioners creates a risk of morbidity and mortality due to cardiovascular disease), justifying their referral to their GP for further diagnosis.

Table 8. Blood values for men and women who underwent screening*

	All screened persons n=4,459		Men n=1,938		Women n=2,521	
	mmol/l*	N (%)	mmol/l*	N (%)	mmol/l*	N (%)
Glucose	5,03		5,15		4,94	
Normal	4,90	4.208 (94,4)	4,98	1.791 (92,4)	4,85	2.417 (95,9)
IFG (6,1-6,9)	6,38	171 (3,8)	6,37	98 (5,1)	6,39	73 (3,0)
Diabetes (>=7,0)	8,95	80 (1,8)	9,25	49 (2,5)	8,47	31 (1,2)
Totaal cholesterol (TC)	5,63		5,53		5,70	
Normal (<6,5)	5,27	3.565 (80,0)	5,22	1.609 (83,0)	5,30	1.956 (77,6)
Increased (>=6,5)	7,07	894 (20,0)	7,04	329 (17,0)	7,09	565 (22,4)
HDL-cholesterol	1,43		1,24		1,57	
LDL-cholesterol	3,53		3,53		3,53	
Triglyceriden	1,44		1,61		1,31	
Ratio TC/HDL cholesterol	4,20		4,70		3,82	
Normal (<4,4 mmol/l)	3,39	2.712 (60,8)	3,60	850 (43,9)	3,30	1.862 (73,9)
Increased (>=4,4 mmol/l)	5,46	1.747 (39,2)	5,56	1.088 (56,1)	4,29	659 (26,1)
NHG-risicotabel*						
Green		3.818 (87,0)		1.464 (76,9)		2.354 (94,7)
Yellow+red		572 (13,0)		440 (23,1)		132 (5,3)

* average values unless otherwise specified.

† in addition to lifestyle advice: green=no medication, yellow=consider medication if other risk factors are present, red= usually requiring medication (M84 in the Netherlands College of General Practitioners standard cardiovascular risk management recommendations).

4.6 Detection rate by action levels

The percentages of men and women with blood values that might indicate type 2 diabetes or impaired fasting glucose (IFG) are shown in the figures below for various age at randomisation and action level categories. The figures compare action level 1 (waist size >=94 cm for men, >=80 cm for women) and action level 2 (waist size >=102 cm for men, >=88 cm for women) for the detection of IFG (Figure 5) and DM (Figure 6). There is a connection with age for both action levels with regard to both IFG and diabetes.

Figure 5. **IFG (impaired fasting glucose) detection rate for different age categories.**

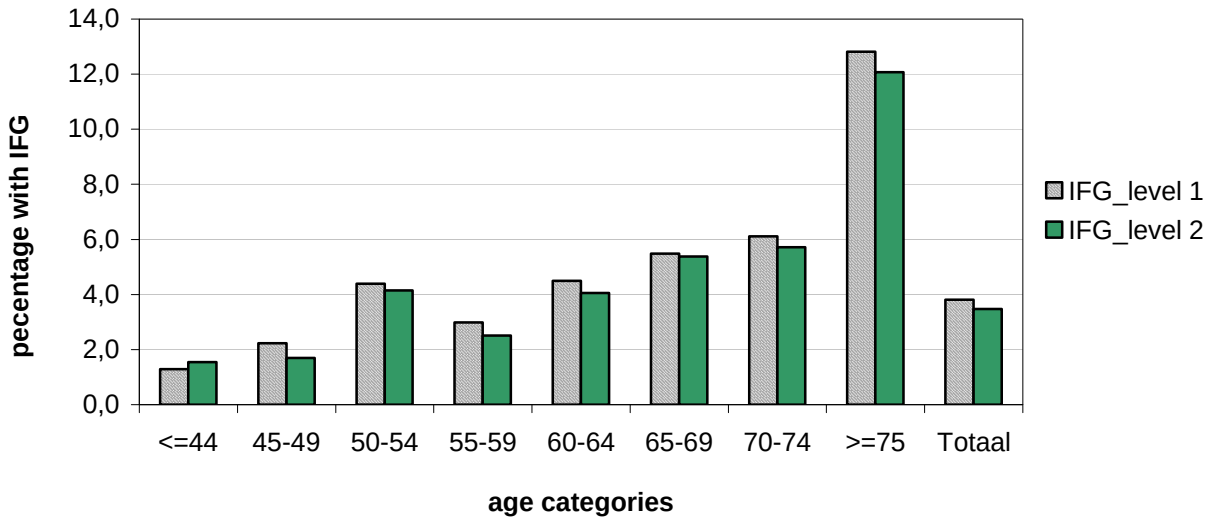
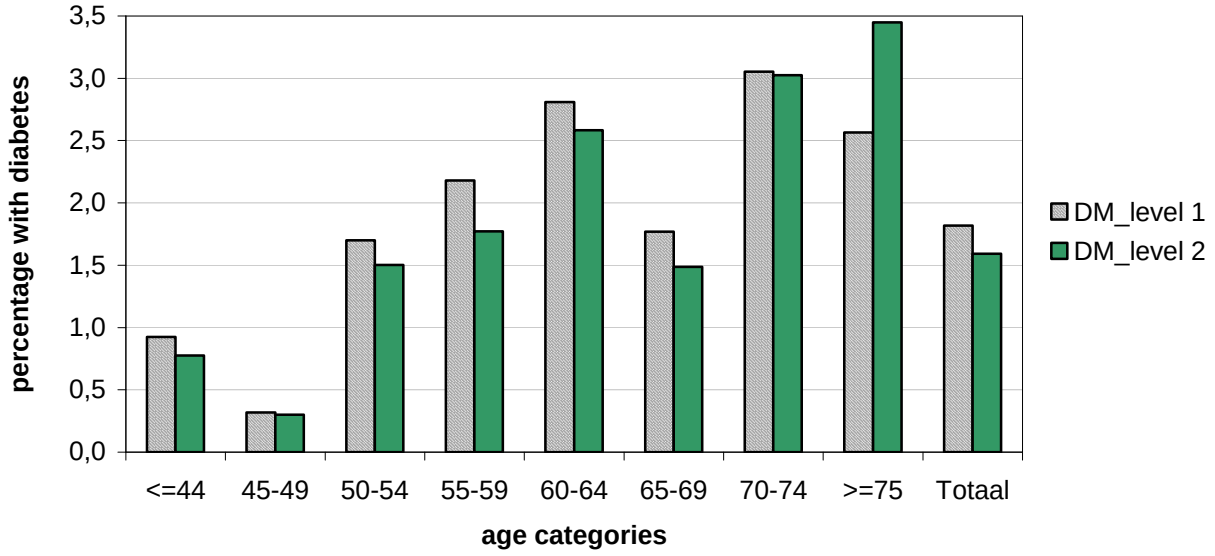


Figure 6. **Type 2 diabetes detection rate for different age categories.**



5. DISCUSSION AND CONCLUSIONS

We submitted our project proposal “Randomised controlled trial of screening for type 2 diabetes mellitus in obese subjects“ to ZonMw in 2005. It was to be a randomised study into the effects of screening on diabetes among individuals with abdominal obesity. The project proposal was examined in detail by four external experts and found to be of high quality and relevance. The Efficacy and Suitability Review subcommittee and the Prevention Programme committee also decided that the study was relevant to the Prevention Programme and of high quality (ZonMw decision taken on 08.05.2005 (2005/10013/ZONMW/mh)). In view of the scale of the project and the associated costs, we suggested first conducting a pilot study with specific feasibility questions among around 20% of the target population and awaiting the results. Specific expectations have already been set down in the application (subsidy application form no. 3082, 2005) which give an insight into the minimum conditions for a possible successful large-scale efficacy study:

1. mailing a tape measure as the first risk test to all people aged between 40 and 75 produces a sufficiently large high-risk study population: we predict that 13.7% of the individuals contacted in this way will fall into the high-risk group *and* be willing to undergo randomisation.
2. the "high risk selection test", in which the individual measures his or her own waist size, is a sufficiently reproducible method: a sub-group should be re-measured by an expert in order to investigate the accuracy of the data.
3. after individuals are assigned at random to the study arm (invitation to screening), a sufficient number of people should attend appointments to have their glucose and lipid levels measured.
4. a considerable proportion of the individuals who are screened should be found to have positive results that had not previously been diagnosed. They could then be referred to their GP for further diagnosis and treatment.

These expectations are not aimed particularly at achieving a high response rate in individual sub-groups (classified according to SES or ethnicity) because the large-scale study will after all be investigating the efficacy of screening, and a sufficiently large number of participants – with a reasonable representation of relevant sub-groups – is essential in order to produce a reliable and valid answer.

Expectations

As indicated above in the 'results' section, the population size for the pilot was determined by the number of records provided by the two local authorities, in which we contacted 15% of the population that we wish to approach in the large-scale project. Nevertheless, all the specific expectations were met in the pilot study in which almost 80,000 people were contacted:

1. 13.4% of the individuals who were initially contacted appeared to be in a high-risk group and were prepared to undergo randomisation (without a reminder invitation), and we showed that if we approached everyone in a one-step procedure we would in future be able to increase this figure to 13.7%.
2. there was a significantly high correlation between self-measured waist size and waist size as measured by paramedics (around r=0.8 for both men and women).
3. 84.1% of the people invited to give fasting blood samples agreed to have blood taken (were screened).
4. 5.6% of these people were found to have undiagnosed impaired glucose metabolism and 13.0% were found to have impaired lipid metabolism, which according to the Netherlands College of General Practitioners risk table presents a risk of cardiovascular morbidity and mortality. So in the end approximately 18.6% of high-risk individuals were referred to their GP.

Response to mailings among all individuals contacted

The response to the mailings was 26% rather than the target figure of 50% (table 2). This could raise doubts as to success in reaching the target group and the feasibility of the study, even though the "overall" final response of 13.4% met our expectations. However, this 26% response is a proportion of all the individuals contacted, not the actual target group for the study (people with abdominal obesity who are at high risk). The eventual proportion of high-risk individuals who agreed to undergo randomisation was in fact an almost exact match for the original objective. 78.2% of respondents fell into the high-risk group (or 74% if we take the other exclusion criteria into account).

Other projects involving the mailing of questionnaires also show that the response can vary markedly depending on the subject and the age group contacted. This makes it difficult to predict response rates. The response rate in an RCT dealing with delayed linguistic development conducted among 10,000 parents of three-year-old children was 75%. When invitations to a trial of screening for prostate cancer were sent to 40,000 men, asking for consent to randomisation, the response rate was 40%. Sending out general questionnaires through the local health authorities for a lung cancer screening project typically produced response rates of around 30%. Our initial estimate of a 50% response to a general questionnaire falls within this range.

Response to mailings among high-risk individuals

For the conduct of the study itself, it has been decided, after consulting local health authorities and the medical ethics committee, that the information accompanying the first questionnaire should also contain detailed information about obesity, waist size, and criteria for elevated risk, diabetes and the trial. For instance: "*Being overweight or obese puts you at greater risk of diabetes. The risk is higher if the excess fat is around the stomach (a lot of fat in the abdominal cavity). That is why this study is concentrating on this high-risk group: men and women with a large waist size. We will select people who are eligible to take part in this trial using the enclosed questionnaire and waist size measurements. That is because these people are at greater risk of diabetes. Would you like to know if you fall into this high-risk group? If so, measure your waist size*".

This contact therefore already contained information about the possibility of taking part in a trial (and so did not just ask people to return a general questionnaire). We found that the logistical conduct of the study was such that we would be likely to generate responses from the high-risk group, and that is clearly what happened. The percentages in the two procedures clearly show the same picture. We observed that the anticipated 50% response rate to the mailing among the target group was certainly feasible, and that as expected we achieved the 13.4% inclusion rate of people with abdominal obesity (definition: waist size of 94 cm or more in men and 80 cm or more in women).

Dispatch methods and costs

One aspect that originally was not to be examined in the pilot study was which method of dispatching the mailings produced the greatest response among high-risk individuals, and what the costs of each method were. As stated above, the beforehand-expected response was obtained using method 1, a one-step procedure in which we asked respondents to consent to take part in research before they knew whether they met the inclusion criteria (table 3). In the remainder of the study we will apply method 1, as it produced the expected inclusion rate of 13.7% (as we anticipated). The costs of dispatch per participant are lower for method 1 than for method 2: the costs per participant in the screening group and the control group are € 5.82 and € 4.58 respectively for method 1 and € 6.67 and € 5.43 for method 2. The total costs for a participant in the screening group, including taking blood samples (the screening) and lab tests, are € 19.32.

Socio-economic characteristics

When assessing the efficacy of a preventive or curative measure, it is often a requirement that the evidence must come from a randomised controlled trial in which the volunteers/participants give their consent beforehand and are then allocated (at random) to either the intervention group or the control group. This always raises the possibility that those who volunteer to take part present a kind of (unintended) self-selected group of those who are contacted. For this pilot study we had the study material specially written in simple Dutch by Bureau Taal, and placed advertisements in local newspapers in the two study towns around the time that the letters were being sent out. We did this to try to ensure that we reached enough people with a low level of educational attainment and people of non-Dutch origin.

We know that response rates from non-Western foreigners is low, especially among those living in (heavily) urbanised areas (Schmeets, 2004). Schmeets conducted a more detailed analysis of responses to the POLS [Permanent Investigation of Living Conditions] study in the fourth-quarter edition of Statistics Netherlands' population trends in 2004, and found that response rates were higher among people of Surinamese and Antillean origin than those of Turkish or Moroccan descent. We observed the same pattern in our pilot study (table 5). Another study carried out by Carlier et al. in Utrecht (Carlier et al, 2007) showed the 'spontaneous response' pattern among people aged between 40 and 65 from these ethnic groups (Surinamese/Antilles 18.8%, Turkish 10.1%, Moroccan 11.7%) to be similar to what we observed in our pilot study among people aged between 40 and 74, where no reminder letters were sent out (table 5: 18.5%, 12.7% and 7.8%) respectively. The final response rates in the Utrecht study were 47.6%, 44.7% and 37.8% respectively, after a reminder letter had been sent (three weeks after the first letter was sent, first reminder) and a reminder telephone call or home visit had been made (five weeks after the first letter was sent, second reminder).

It is impossible to say whether there might be an ethnic sub-group (fewer than 5%) to which this conclusion would not generally apply. There is insufficient power to perform sub-group analyses for such small sub-groups. Of course we want to examine the issue of abdominal obesity and diabetes in these sub-groups, but this was not the aim of the pilot phase. If the objective of this pilot study had been to obtain exactly the same response rates for every conceivable ethnic sub-group in Capelle/Dordrecht, then we would have had all the information material translated into the relevant languages at this stage, or sent out additional reminders. It is clear that our pilot study of around 80,000 individuals included a sufficiently representative target group, despite (or thanks to) national campaigns. We know that attention remains focused on diabetes and obesity at national level via initiatives such as the "Kijk op Diabetes" campaign, with the aim of reducing the number of undiagnosed cases of diabetes. Even so, only 8.2% of respondents said that they had taken part into a study into diabetes or cardiovascular disease in the past six months (table 9).

Reliability of waist size measurements

In order to check the reliability of self-reported or self-measured waist size figures, the participants had to fill in the figures twice on the questionnaire, and employees of Star-MDC re-measured the waist sizes of a small sample (n=160) according to the same protocol that was sent out with the mailings. Measuring waist size with the 160-cm tape measure sent out with the mailings was sufficiently effective up to a point. This is shown by the high percentage of people (81%) whose two waist size figures reported fell into the same category, and the Cohen's kappa figure of 0.64. It is difficult to compare the findings with previously published data on the frequency distribution of such self-measured waist sizes as the data we have here relates mainly to people who are overweight or obese. We also find good correlations between self-reported data and externally validated measurements (figure 3). It might be useful to take weight or BMI into account as well just above the 80cm cut-off point (figure 4).

We chose cut-off points of >=94 cm for men and >= 80 cm for women instead of >=102 cm and >=88 cm as we thought that these less strict cut-off points would be more likely to include people of Asian origin and elderly

people. Table 8 shows that a high percentage (72.5% of men and 83.7% of women) are eligible to take part in the study because of the lower cut-off points ('action level 1'). 53.5% of the men and approximately 75% of the women who underwent randomisation fall into the action level 2 category.

Aspects that have not yet been covered

A small number of questions still remain to be addressed: the extent of opportunistic screening in the control group (contamination) and the workload involved in the follow-up of patients referred to their GP. We cannot draw any conclusions on that because the first invitations for the screening test (blood sample for fasting glucose measurement) were sent out in mid-October. We will perform a non-response analysis (in writing or by telephone) to try to investigate the reasons why individuals did not respond: age, known DM cases, education, height/weight, country of birth, possible religious/cultural reasons, health, comprehensibility of the information, etc. We intend to do this nine to twelve months after sending out the questionnaire. We are currently occupied with drawing up the questionnaire.

6 RECOMMENDATION

The aim of the large-scale pilot study was to ascertain whether continuing this research on a larger scale was justified by recruitment, selection, SES, compliance, and the percentage of newly diagnosed abnormalities. We found no reason for abandoning the work in the light of any of these factors, rather the reverse. We have identified a substantial and sufficiently large high-risk group and included them, covering the entire socio-economic and ethnic spectrum. The initial response among the high-risk target group was above the expected figure of 50%. There were enough individuals with demonstrable undiagnosed impaired glucose and lipid levels (5.6% and 13% respectively) in the high-risk group for whom both primary and secondary prevention measures could be effective. We therefore recommend that the project should continue in order to answer the question of whether screening for type 2 diabetes in a high-risk group is an effective way of reducing diabetes-related morbidity and mortality. The project is an important contribution to the policy of screening for diabetes in high-risk groups, and to any policy that may be devised on opportunistic screening.

7 LITERATURE

- Carlier B.E., van Ameijden E.J.C., van den Brink C.L., Bouwman-Notenboom A.J., van Bergen A.P.L. Survey study among disadvantaged groups: non-response and internal validity. Utrecht local health authority, February 2007.
- Schmeets H. Response of first-generation immigrants to the POLS. Population trends, 4th quarter of 2004, Statistics Netherlands.
- Schouten G, Kuilman M. 2005 health survey - Health in eight towns in the Rotterdam-Rijnmond health authority region. Rotterdam-Rijnmond local health authority, June 2007.
- Terpstra J.S., Sanavro F.L., Leeuwenburg J. Zuid-Holland Zuid 2006 Health Monitor. Zuid-Holland Zuid local health authority, June 2006.