

Incidence of Type 2 Diabetes in the Randomized Multiple Risk Factor Intervention Trial

George Davey Smith, DSc; Yiscah Bracha, MS; Kenneth H. Svendsen, MS; James D. Neaton, PhD; Steven M. Haffner, MD; and Lewis H. Kuller, MD, for the Multiple Risk Factor Intervention Trial Research Group*

Background: Weight loss and increased physical exercise reduce the risk for diabetes in people with impaired glucose tolerance. Randomized trial evidence on the effect of these interventions on people without impaired glucose tolerance is lacking.

Objective: To examine the influence of a comprehensive intervention program on the risk for developing diabetes in men without impaired glucose tolerance and in a post hoc subgroup analysis by baseline cigarette smoking status.

Design: Randomized, controlled trial.

Setting: 22 clinical centers for the Multiple Risk Factor Intervention Trial (MRFIT).

Participants: 12 866 men age 35 to 57 years at risk for cardiovascular disease were randomly assigned to either a special intervention or usual care group and followed for 6 to 7 years; this report focuses on 11 827 men without diabetes or impaired glucose tolerance at entry for whom follow-up glucose measurements were available.

Measurements: Cardiovascular disease risk factors, fasting blood glucose levels, and diabetes medication history were assessed before randomization and annually.

Intervention: Men in the special intervention group were counseled to change diet (reduce saturated fat, cholesterol, and calorie intake), to stop smoking, and to increase physical activity. Blood

pressure was treated more intensively in the special intervention group than in the usual care group.

Results: 11.5% of the special intervention group and 10.8% of the usual care group developed diabetes over 6 years of follow-up (hazard ratio, 1.08 [95% CI, 0.96 to 1.20]). The special intervention–usual care hazard ratio for diabetes was 1.26 (CI, 1.10 to 1.45) among smokers (63%) and 0.82 (CI, 0.68 to 0.98) among nonsmokers (37%). These estimates differed significantly ($P = 0.0003$). Weight gain after smoking cessation and the use of antihypertensive drugs may have counterbalanced the beneficial effect of the lifestyle intervention for the special intervention group smokers, while the lifestyle intervention was beneficial among nonsmokers.

Limitations: Principal findings are based on a post hoc subgroup analysis.

Conclusions: In nonsmokers, an intervention program that included nutrition counseling to produce reductions in weight, serum cholesterol, and (along with antihypertensive medication) blood pressure reduced the risk for diabetes.

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For author affiliations, see end of text.

*For a complete list of Multiple Risk Factor Intervention Trial investigators, see the following: Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. *JAMA.* 1982;248:1465-77. [PMID: 7050440]

This trial is registered as NCT00000487 on <http://clinicaltrials.gov>.

Epidemiologic studies have identified several potentially modifiable risk factors for type 2 diabetes mellitus, including obesity, a diet in which a high proportion of calories comes from fat, and low levels of physical activity (1–7). Authorities have advocated that trials should test promising hypotheses about the primary prevention of type 2 diabetes (1). Randomized intervention studies have demonstrated that, among those who already have impaired glucose tolerance, interventions that promote weight loss and increased exercise can reduce the risk for incident diabetes (8–10). However, interventions should occur before at-risk individuals develop impaired glucose tolerance. A 2-year randomized trial of diet, exercise, or both in individuals with a parental history of diabetes showed a statistically imprecise lower risk for developing diabetes in the intervention group (11). To test such a hypothesis in groups who do not necessarily have a parental history of diabetes would be expensive.

Strategies proposed for the primary prevention of type 2 diabetes include weight reduction, reduced dietary fat intake, and increased exercise (2, 4, 7). These interventions are similar to those developed for preventing coronary

heart disease; therefore, examination of type 2 diabetes incidence rates in coronary heart disease prevention trials can provide preliminary evidence on the potential of such interventions to reduce type 2 diabetes risk.

The Multiple Risk Factor Intervention Trial (MRFIT) enrolled 12 866 middle-aged men at high risk for coronary heart disease and delivered either special intervention or usual care over 6 to 7 years. The researchers obtained fasting glucose values yearly, and participants self-reported

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Context

Weight loss and exercise decrease the development of diabetes in people with impaired glucose tolerance, but the effectiveness of these interventions in people with normal glucose tolerance is unknown.

Contribution

Using data from a large randomized, controlled trial of cardiovascular disease prevention in men, the investigators show that participants with normal glucose tolerance at baseline developed diabetes at similar rates whether they received the lifestyle intervention or usual care. However, the intervention was associated with lower risk of diabetes among nonsmokers.

Implications

While diet and exercise may reduce the development of diabetes in nonsmokers with normal glucose metabolism at baseline, this benefit was not apparent among smokers.

—The Editors

their use of insulin or oral hypoglycemic agents. The glucose values and reports of diabetes medication use enable estimation of diabetes incidence during the trial. Previous reports from MRFIT have described risk factors for the development of diabetes in the usual care group (12) and the risk for death associated with incident diabetes in the combined special intervention and usual care groups (13). In this paper, we compare the incidence of diabetes in the intervention and control groups of the MRFIT, report on an unexpected subgroup finding related to baseline cigarette smoking status, and explore reasons for the different results among smokers and nonsmokers.

METHODS**Procedures**

Detailed descriptions of the MRFIT have been published (14–17). Briefly, between 1973 and 1976, the MRFIT investigators screened 361 662 men for eligibility at 22 U.S. clinical centers. Of this group, 12 866 men age 35 to 57 years were randomly assigned: 6428 men to the special intervention group and 6438 men to the usual care group.

Screening occurred at 3 visits. At the first screening visit, investigators assessed the risk for coronary heart disease by using measurements of serum cholesterol level, diastolic blood pressure, and self-reported cigarette smoking (14). Men who were in the upper 15% (changed to 10% after one third of the screening was completed) of risk were invited to attend a second screening visit. Because of the eligibility criteria used in the MRFIT, the usual relationships among these risk factors were modified. For example,

nonsmokers had to have higher blood pressure and lipid levels on average than smokers to be eligible for the trial.

At the second screening visit, a blood sample was taken after an overnight fast. A central laboratory at the Institute of Medical Sciences in San Francisco, California, analyzed the blood samples by using a protocol previously described (18) and measured serum glucose in the fasting sample and in a sample taken 1 hour after a 75-g oral glucose load.

The MRFIT also measured height and weight (after the patient had disrobed). Individuals with body weight 150% or more of desirable weight were excluded from the trial (defined as 0.9 of the average for men of the same height in the 1960–1962 National Health Examination Survey [19]). We used body mass index (BMI) as the measure of relative weight in our report.

Men without evidence of cardiovascular or other life-threatening diseases were invited to attend a third screening visit. At this visit, eligible men who consented to the trial were randomly assigned.

All participants had annual examinations for at least 6 years. A fasting blood sample was taken at each annual examination, from which serum glucose concentration and plasma lipid levels were measured. In addition, at the sixth annual visit, a blood sample taken 1 hour after a 75-g oral glucose load was obtained. At each annual examination, participants were asked whether a physician had told them that they had diabetes at any time in the previous 12 months. Each participant was also asked whether he was using insulin or oral hypoglycemic agents.

In the MRFIT, 24-hour dietary recalls were obtained at baseline and during follow-up (20, 21). We cited data from baseline and year 6 in our report.

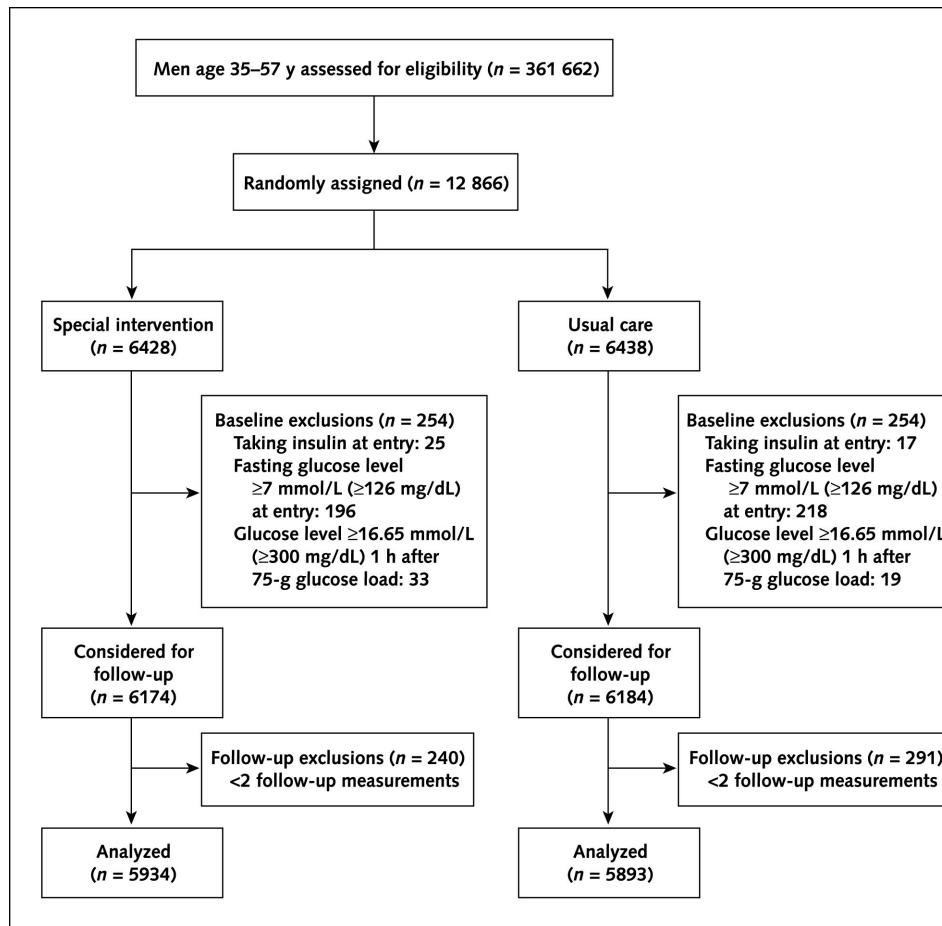
Intervention

Details of the intervention program of the MRFIT have been reported (16, 22). Briefly, the special intervention group received nutritional counseling that was aimed at reducing saturated fat and dietary cholesterol consumption and increasing polyunsaturated fat intake. Smokers participated in a behavioral intervention program aimed at cessation. In men at or more than 115% of desirable weight, reductions in caloric intake and increases in moderate physical activity were recommended. Elevated blood pressure was treated pharmacologically according to a stepped-care protocol that started with 50 mg of chlorthalidone or hydrochlorothiazide if weight reduction and moderate salt restriction did not achieve the desired blood pressure goals.

Definition of Diabetes

The definition of incident diabetes followed the American Diabetes Association (ADA) guidelines (23). With this definition, a participant was considered to have developed diabetes if at any annual visit the fasting glucose level was 7 mmol/L or greater (≥ 126 mg/dL) or the participant reported taking insulin or oral hypoglycemic agents. Use of

Figure. Description of study exclusions.



a single fasting glucose determination to designate diabetic participants is consistent with the ADA criteria for epidemiologic studies.

Exclusions

The MRFIT attempted at baseline to exclude men with identified diabetes from the trial. The trial excluded individuals who were using hypoglycemic drugs, as well as those who were not being treated but who exhibited clinical symptoms of hyperglycemia (15). Despite these exclusion criteria, the trial included 42 men who reported (without confirmation) taking insulin, 414 men with a baseline fasting glucose level of 7 mmol/L or greater (≥ 126 mg/dL), and 52 men with a glucose level of 16.65 mmol/L or greater (≥ 300 mg/dL) 1 hour after a 75-g oral glucose load. We excluded these 508 men and an additional 531 men (291 in the usual care group and 240 in the special intervention group) with fewer than 2 fasting glucose values throughout the trial from our analyses, leaving 11 827 men (5893 in the usual care group and 5934 in the special intervention group) who, by our criteria, were at risk for developing diabetes over the next 6 years (Figure).

Statistical Analysis

We used time-to-event methods appropriate for interval-censored data to compare incidence of diabetes in the special intervention and usual care groups (24). We estimated the cumulative percentage of patients developing diabetes, assuming that participants at risk who did not attend an annual visit did not meet our criteria for diabetes. We used proportional hazards regression models to study the influence of baseline predictors on hazard ratio estimates and to investigate treatment by subgroup interactions. We also used these models to study the influence of risk factor changes on the incidence of diabetes and on special intervention–usual care hazard ratios. We checked the proportional hazards assumption by including a covariate corresponding to the interaction of failure time and special intervention or usual care. In these models, we updated risk factor levels (for example, BMI, use of antihypertensive drugs, and smoking status) annually and considered them to be time-dependent covariates. With this approach, we considered the latest values of risk factors (those immediately preceding diabetes) and baseline levels as predictors. We also used longitudinal regression models for binary

Table 1. Incidence of Type 2 Diabetes after 6 Years of Follow-up by Baseline Cigarette Smoking Status and Treatment Group*

Group	Special Intervention Group		Usual Care Group		Hazard Ratio (95% CI)
	Patients, n	Events, n (%)	Patients, n	Events, n (%)	
Overall	5934	666 (11.5)	5893	616 (10.8)	1.08 (0.96–1.20)
Smokers	3762	453 (12.4)	3748	364 (10.1)	1.26 (1.10–1.45)
Nonsmokers	2172	213 (10.0)	2145	252 (12.0)	0.82 (0.68–0.98)

* $P = 0.0003$ for smoking–treatment interaction. Cumulative incidence at 6 years.

data (25). With these models, participants could be classified as diabetic on several annual visits or at 1 annual visit and not the next.

We used analysis of variance with covariates corresponding to baseline level of the factor being considered to compare risk factor levels at 6 years for special intervention and usual care men, both overall and according to baseline cigarette smoking status. With these models, we also investigated the interaction between treatment and smoking status. Both time-to-event analyses and analyses of variance are stratified by clinical center. We performed all analyses by using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The National Heart, Lung, and Blood Institute supported this work. A member of the funding source sits on the MRFIT Editorial Committee. Apart from providing editorial advice, this member had no role in the reporting of the data.

RESULTS

Diabetes Incidence by Treatment Group and Cigarette Smoking Status at Baseline

As previously reported (16), the special intervention and usual care groups were similar at baseline. Average fasting and 1-hour glucose measurements at baseline were 5.4 mmol/L (97.5 mg/dL) and 9.14 mmol/L (164.6 mg/dL), respectively, and 41% of patients had a fasting glucose level between 5.55 mmol/L (100 mg/dL) and 6.94 mmol/L (125 mg/dL) at entry. Ninety percent of participants had 5 or 6 fasting glucose level measurements during follow-up (91% in the special intervention group and 89% in the usual care group), and an additional 4% in each group had 4 glucose measurements.

Table 1 summarizes the 6-year incidence of diabetes by treatment group. A total of 666 men in the special intervention group and 616 men in the usual care group met the criteria for diabetes during follow-up (hazard ratio, 1.08 [95% CI, 0.96 to 1.20]; $P = 0.20$ for log-rank statistic).

Among participants who did not smoke cigarettes at entry, the incidence of diabetes was 18% lower in the special intervention group than in the usual care group (10.0% vs. 12.0%; $P = 0.03$ for log-rank test). In contrast, among participants who smoked cigarettes at entry, diabetes incidence was higher among special intervention than

usual care participants (12.4% vs. 10.1%; $P = 0.001$). Hazard ratio (special intervention–usual care) estimates for nonsmokers (hazard ratio, 0.82 [CI, 0.68 to 0.98]) and smokers (hazard ratio, 1.26 [CI, 1.10 to 1.45]) significantly differed ($P = 0.0003$). No evidence suggested that the proportional hazards assumption did not hold for the overall group or the smoking subgroups.

A statistically robust treatment by baseline smoking status interaction was also present with use of a more stringent definition of diabetes that required 2 consecutive fasting glucose level measurements of 7.77 mmol/L or greater (≥ 140 mg/dL) or use of medication for diabetes ($P < 0.0001$ for interaction) (12). With this definition, the hazard ratios (special intervention–usual care) for nonsmokers and smokers were 0.50 (CI, 0.35 to 0.71) and 1.37 (CI, 1.07 to 1.76), respectively. Interactions were found for the percentage of participants using drugs for diabetes by year 6 ($P = 0.005$), for fasting glucose levels at year 6 ($P < 0.0001$), and for 1-hour glucose levels at year 6 ($P = 0.014$).

We performed an analysis that included an additional 288 participants who had 1 follow-up glucose level measurement but not 2 or more follow-up glucose level measurements. For these 12 115 participants (we excluded only 243 participants—118 in the special intervention group and 125 in the usual care group—with no follow-up measurements), the interaction between treatment group and baseline smoking status was essentially unchanged ($P = 0.0003$). For this same cohort of participants, we used a longitudinal regression model to estimate the relative odds of diabetes at each annual visit. This model used all follow-up data available and considered changes in diabetes status over follow-up. Averaged over follow-up, the relative odds of diabetes (special intervention–usual care) was 1.56 (CI, 1.14 to 2.14) for smokers and 0.67 (CI, 0.52 to 0.87) for nonsmokers ($P < 0.0001$ for interaction).

Because of randomization and the large number of participants, special intervention and usual care nonsmokers and special intervention and usual care smokers had nearly identical average risk factor levels (data not shown). However, partly because of the eligibility criteria used in the MRFIT, smokers' and nonsmokers' baseline risk factor characteristics considerably differed (**Appendix Table 1**, available at www.annals.org). By trial design, nonsmokers had to have higher blood pressure and lipid levels on average to be eligible for the trial. Weight and BMI were also

significantly higher among nonsmokers than smokers. Most elements of the diet also differed between nonsmokers and smokers at baseline.

To determine whether the interaction between treatment group and smoking status for diabetes could be explained by differences between smokers and nonsmokers in the other risk factors used to select participants for the trial (that is, to assess the possibility that smoking status may be incorrectly identified as the effect modifier), we performed a regression analysis with interaction terms corresponding to treatment group and cholesterol level and treatment group and diastolic blood pressure along with the interaction term for treatment group and smoking status. This did not materially alter the *P* value for the interaction between treatment group and smoking status (*P* = 0.0004).

We also performed analyses according to baseline fasting glucose level (<5.5 mmol/L [<100 mg/dL] and ≥ 5.5 mmol/L [≥ 100 mg/dL]). Among both smokers and nonsmokers, for both the special intervention and usual care groups, the incidence of diabetes was 4- to 5-fold higher for those with baseline fasting glucose levels of 5.5 mmol/L or greater (≥ 100 mg/dL) than in those with levels less than 5.5 mmol/L (<100 mg/dL). However, the smoking by treatment group interaction did not vary by baseline fasting glucose level (*P* = 0.73 for 3-way interaction). For example, special intervention–usual care hazard ratios for nonsmokers were 0.86 for those with baseline fasting glucose levels of 5.5 mmol/L or greater (≥ 100 mg/dL) and 0.76 for those with baseline fasting glucose levels less than 5.5 mmol/L (<100 mg/dL). Among smokers, the corresponding hazard ratios were 1.23 and 1.21, respectively. We performed similar analyses according to age (35 to 44 years and 45 to 57 years) and 1-hour glucose levels (<11.1 mmol/L [<200 mg/dL] and ≥ 11.1 mmol/L [≥ 200 mg/dL]), and the findings were similar (that is, the interaction between smoking and treatment group was essentially unaltered).

We also performed analyses according to the number of cigarettes smoked per day reported at entry. Hazard ratios for those reporting 1 to 19, 20 to 39, and 40 or more cigarettes per day were 0.81, 1.29, and 1.34, respectively (*P* = 0.22 for interaction between treatment group and number of cigarettes smoked).

Influence of Risk Factor Intervention on Incidence of Diabetes

To investigate whether any aspects of the intervention program for the special intervention group might have influenced the differential effect of treatment on diabetes according to smoking status, we compared risk factor levels after 6 years in the special intervention and usual care groups according to baseline smoking status (Appendix Table 2, available at www.annals.org). The intervention effect on blood pressure and plasma cholesterol level varied according to smoking status. For both risk factors, the effect of intervention was greater among nonsmokers than smokers. However, for both risk factors, the intervention for special intervention participants resulted in statistically robust lower risk levels at 6 years for both nonsmokers and smokers. Likewise, average differences between the special intervention and usual care groups for BMI, fat intake, dietary cholesterol intake, and total carbohydrates intake were greater after 6 years among nonsmokers than smokers. For each of these risk factors, the trends were similar for nonsmokers and smokers, but the intervention effect was greater among nonsmokers than smokers. The only risk factor that showed a potentially greater effect of the intervention among smokers was a reduced number of alcoholic drinks consumed per week.

Changes in BMI, use of antihypertensive drugs, and cigarette smoking cessation were important determinants of the development of diabetes in the special intervention and usual care groups (Table 2). In proportional hazards models that also included baseline covariates previously identified as predictors of diabetes in the usual care group (12), among both nonsmokers and smokers at entry (for both special intervention and usual care participants), BMI decreases were associated with a reduced risk for diabetes and use of antihypertensive drugs was associated with an increased risk for diabetes. Among smokers at entry (for both special intervention and usual care participants), smoking cessation was associated with an increased risk for diabetes. Change in BMI only partially explained the increased risk for diabetes associated with smoking cessation (Table 2). In a model such as that shown in Table 2 but with BMI change excluded, the hazard ratios associated with quitting smoking were 1.38 (CI, 1.13 to 1.67) for the

Table 2. Summary of Cox Regression Models Smoking Status and Intervention Group for the Association by Change in Body Mass Index, Use of Antihypertensive Drugs, and Smoking Cessation and the Development of Diabetes*

Variable	Hazard Ratio for Nonsmokers (95% CI)		Hazard Ratio for Smokers (95% CI)	
	Special Intervention Group	Usual Care Group	Special Intervention Group	Usual Care Group
BMI (1 kg/m ² decrease)	0.75 (0.70–0.81)	0.84 (0.78–0.90)	0.83 (0.79–0.88)	0.81 (0.77–0.86)
Use of antihypertensive drugs (1 = yes; 0 = no)	4.12 (2.66–6.40)	1.84 (1.40–2.44)	2.22 (1.76–2.80)	2.14 (1.69–2.71)
Smoking cessation (1 = yes; 0 = no)	NA	NA	1.21 (0.99–1.47)	1.35 (1.06–1.72)

*All models include baseline covariates corresponding to age, race, family history of diabetes, diastolic blood pressure, serum cholesterol level, and cigarettes smoked per day for smokers. BMI = body mass index; NA = not applicable.

Table 3. Influence of Covariate Adjustment on Hazard Ratios for the Special Intervention and Usual Care Groups for the Development of Diabetes by Baseline Smoking Status*

Variable	Hazard Ratio (95% CI)		
	Nonsmokers	Smokers	All Participants
No covariates	0.82 (0.68–0.98)	1.26 (1.10–1.45)	1.08 (0.96–1.20)
Baseline covariates adjustment	0.79 (0.66–0.95)	1.27 (1.10–1.46)	1.07 (0.95–1.19)
Adjustment for change in BMI	0.97 (0.80–1.18)	1.34 (1.17–1.55)	1.19 (1.06–1.33)
Adjustment for use of antihypertensive drugs	0.68 (0.56–0.82)	1.13 (0.98–1.30)	0.94 (0.84–1.05)
Adjustment for smoking cessation†	NA	1.14 (0.99–1.32)	0.99 (0.89–1.11)
Adjustment for change in BMI and use of antihypertensive drugs	0.83 (0.68–1.01)	1.19 (1.03–1.38)	1.05 (0.93–1.17)
Adjustment for smoking cessation and change in BMI†	NA	1.25 (1.08–1.44)	1.13 (1.01–1.27)
Adjustment for smoking cessation† and use of antihypertensive drugs	NA	1.03 (0.89–1.19)	0.89 (0.79–0.99)
Adjustment for smoking cessation† and change in BMI and use of antihypertensive drugs	NA	1.13 (0.97–1.31)	1.00 (0.89–1.13)

* BMI = body mass index; NA = not applicable.

† Applicable only for baseline smokers; all models also include baseline covariates.

special intervention group (vs. 1.21 after adjustment for change in BMI) and 1.64 (CI, 1.30 to 2.07) for the usual care group (vs. 1.35 after adjustment for change in BMI). More special intervention participants quit smoking than usual care participants (Appendix Table 2), and BMI increased from baseline for both special intervention and usual care participants who quit smoking by 6 years (increase of 0.55 kg/m² for special intervention and increase of 1.04 kg/m² for usual care). For men who did not quit smoking, BMI decreased by 0.22 kg/m² for special intervention participants and increased by 0.04 kg/m² for usual care participants.

To examine the potential contribution of risk factor differences during follow-up to the special intervention and usual care differences in the development of diabetes, we compared different proportional hazards models for the time until diabetes diagnosis, with adjustment for factors shown in Table 2, separately and overall (Table 3). Because of the greater decreases in BMI for the special intervention group than the usual care group during follow-up, adjustment for changes in BMI during follow-up tended to increase hazard ratio estimates. Among nonsmokers, the hazard ratio increased from 0.82 to 0.97, suggesting that the favorable effect of the special intervention on diabetes incidence resulted from more favorable weight changes. Adjustment for the use of antihypertensive drugs attenuated the increased risk among the special intervention group, suggesting that the greater use of antihypertensive drugs in this group led to some increase in the risk for diabetes. In line with this, adjustment for antihypertensive drug use among baseline nonsmokers resulted in the special intervention–usual care hazard ratio shifting further from unity; among smokers, the hazard ratio shifted closer to 1.0. The counteracting effects of BMI and use of antihypertensive drugs resulted in hazard ratios similar to those obtained in models with no adjustment.

Among baseline smokers, adjustment for both smoking cessation and antihypertensive drug use attenuated the special intervention risk to 1.03 (CI, 0.89 to 1.19). Among all participants (smokers and nonsmokers), such adjust-

ment resulted in a hazard ratio of 0.89 (CI, 0.79 to 0.99). Additional adjustments for changes in a wide range of nutrient intakes (fiber, caffeine, vitamins, folic acid, and minerals) and factors shown in Appendix Table 2 (available at www.annals.org) did not alter these estimates (data not shown).

To further explore the increased risk for diabetes among smokers in the special intervention group compared with smokers in the usual care group, we considered whether the increased risk for diabetes among special intervention compared with usual care participants varied according to smoking cessation at 6 years. The special intervention–usual care hazard ratios for those who did not quit smoking and those who did quit smoking were 1.23 and 1.00, respectively ($P = 0.20$ for difference).

DISCUSSION

Among nonsmokers at baseline in the MRFIT, the intervention program was associated with an 18% reduction in the incidence of diabetes over a 6-year follow-up period compared with those randomly assigned to usual care. Among smokers at baseline, however, the special intervention group had a 26% greater risk for diabetes than the usual care group. The relative differences in diabetes incidence between the special intervention and usual care group are significantly different for baseline smokers and nonsmokers ($P = 0.0003$). Since such an interaction was not postulated at the time our investigation began, it should be interpreted cautiously (26).

The risk factor selection criteria for the MRFIT, which were based on a combination of smoking, blood pressure, and serum cholesterol level, led to very different risk factor profiles in smokers and nonsmokers. Nonsmokers had higher levels of blood pressure and serum cholesterol than smokers. Nonsmokers also had higher levels of BMI and fasting glucose than smokers (Appendix Table 1). Compared with smokers in the MRFIT, nonsmokers were more likely to exhibit evidence of syndrome X (27) (or the metabolic syndrome [28]), suggesting that they were initially at higher risk for developing diabetes compared with the

smokers. In the usual care group, nonsmokers experienced a higher incidence of diabetes than smokers (12), which supports the presumption that the MRFIT selection criteria led to an initially higher risk for diabetes in this particular group of nonsmokers. This does not suggest, however, that nonsmokers in general are at higher risk for diabetes than smokers; indeed, some prospective and laboratory studies indicate that smoking may increase the risk for diabetes (29, 30).

Since the nonsmokers in the MRFIT seem to have been initially at higher risk for diabetes because of the selection criteria, the data suggest that in a group at high risk, intervention that includes nutritional counseling aimed to produce reductions in blood pressure, weight, and serum cholesterol level may be effective in preventing diabetes. This is supported by the observation that weight loss during the trial was associated with reduced diabetes incidence in both baseline nonsmokers and smokers. Among nonsmokers, weight loss was greater in the special intervention group than in the usual care group, and the difference in diabetes incidence (among nonsmokers) in the study groups was substantial (10.0% vs. 12.0%) considering the risk for morbidity and mortality associated with diabetes. For example, for this cohort, we recently reported cardiovascular disease mortality over a median post-trial follow-up of 18.5 years for those who developed diabetes during the trial (13). We defined 4 mutually exclusive groups and those with fasting glucose levels less than 7 mmol/L (<126 mg/dL), which included the reference group. Hazard ratios were 2.07 ($P < 0.001$) for men prescribed insulin or an oral hypoglycemic agent at any time during the trial, 1.65 ($P < 0.001$) for those with a fasting glucose level of 7.81 mmol/L or greater (≥ 140 mg/dL), and 1.19 ($P = 0.03$) for those with a fasting glucose level between 7 mmol/L (126 mg/dL) and 7.7 mmol/L (139 mg/dL).

Findings in Other Multiple Risk Factor Intervention Trials

Several other randomized risk factor intervention trials have been performed with primary prevention of cardiovascular disease as the intended outcome. Few trials have reported their findings with respect to glucose tolerance and diabetes. These trials did not select participants for impaired glucose tolerance; in fact, like the MRFIT, most trials have used clinical diabetes or elevated fasting glucose level as exclusion criteria.

The Oslo Study Group trial (31) was similar in design to the MRFIT. The intervention produced reductions in several components of syndrome X, including weight and both fasting and nonfasting triglyceride levels. In a subsample, an oral glucose tolerance test was done 3 years after the intervention started (32). Serum insulin response to the glucose tolerance test was reduced in the intervention group compared with the control group. In the Family Heart Study (33), investigators randomly assigned lifestyle

counseling to families registered with British general practitioners. For middle-aged men, but not women, random blood glucose levels were lower after the intervention among those assigned to lifestyle counseling compared with the control group. However, the prevalence of blood glucose levels greater than 10 mmol/L (>180.2 mg/dL) was not influenced by the intervention, and the proportion with reported diabetes was actually slightly (but not statistically robustly) higher in the intervention than control group. In the study by Miettinen and colleagues (34), an intervention targeting weight loss, decreased saturated fat intake, decreased alcohol consumption, increased physical activity, smoking cessation, and increased physical activity resulted in greater weight loss in the intervention group than in the control group. No difference in glucose tolerance during a 1-hour oral glucose tolerance test was seen (34). The high level of antihypertensive drug therapy in the intervention group may account for this, since several antihypertensive agents lead to a worsening of glucose tolerance (35).

The findings from trials of several cardiovascular disease risk factor interventions are limited and mixed. Trials of weight loss and aerobic exercise alone or in combination are more consistent in demonstrating improved glucose tolerance. In a randomized trial (36), Katznel and colleagues allocated obese men to a weight loss program, aerobic exercise, or no intervention (36). Although the high dropout rate limits the robustness of the findings, weight loss intervention seems to improve glucose tolerance with similar but lesser improvement from exercise. Among Swedish middle-aged men randomly assigned to dietary advice, exercise, both dietary advice and exercise, or no intervention, enhanced insulin sensitivity was evident in all the intervention groups, congruent with the reduction in BMI produced by the intervention (37, 38). In monkeys, caloric restriction has also been shown to improve glucose tolerance (39, 40). Thus, if weight loss is produced or exercise is increased, glucose tolerance can be improved.

Trials among Participants with Impaired Glucose Tolerance

Several small randomized trials of dietary and exercise interventions among people with impaired glucose tolerance produced mixed results (41–46), while a nonrandomized study suggested considerable benefit for such an intervention package (47). A change in dietary patterns from westernized to traditional forms seems to improve glucose tolerance in glucose-intolerant Australian aborigines (48) and native Hawaiians (49), consistent with the considerable bulk of evidence suggesting that traditional lifestyles involving high levels of physical activity and diets with low-energy density are associated with lower levels of insulin resistance (50). More recently, better evidence from Chinese (8), Finnish (9), and U.S. (10) randomized trials suggests that lifestyle modification can substantially reduce the risk for developing diabetes among people with im-

paired glucose tolerance. Risk reductions were between 30% and 60%. The initial and sustained weight loss in the Finnish and U.S. trials were greater—although not substantially greater—than those among the nonsmokers in our study. In the Finnish (9) and U.S. (10) trials, only 10% and 7% of participants, respectively, were smokers at baseline. Therefore, the nonsmokers in our trial are similar to the overall study samples in these trials. The similarity of effect of intervention in these studies with the effect among nonsmokers in our study suggests that the benefits among people with impaired glucose tolerance are also seen among individuals who are not yet glucose-intolerant.

Conclusions

In a review of the primary prevention on type 2 diabetes mellitus (7), it was stated that intervention before the development of impaired glucose tolerance would be optimal. However, Knowler and colleagues state that “unfortunately, there are no data to support this hypothesis and it would be difficult to test because the costs of clinical trials, in terms of size and duration, might be prohibitive” (7). The Multiple Risk Factor Intervention Trial provides some data on this issue. Among nonsmokers at baseline, an 18% reduction in risk for ADA criteria defined diabetes consequent from an intervention promoting dietary change and increased exercise was seen (with greater reductions for diabetes defined in alternative ways). Because of the selection criteria used for the MRFIT, these men are at a higher risk for developing diabetes than an unselected general population sample (16). This remains a primary prevention situation, however, since the risk for developing diabetes among these men is still considerably lower than that among a group of already glucose-intolerant men. It is probably justified to generalize the findings from this group of men to the broader population and to consider the findings from the MRFIT as demonstrating that primary prevention activities may lead to an important reduction in diabetes risk among nonsmokers and, given the considerable importance of diabetes as a cause of morbidity, mortality, and health service expenditure, an important beneficial population effect.

Reasons for the increased risk for diabetes associated with the intervention among baseline smokers are unclear. Adjustment for antihypertensive drug use attenuated the increased risk in the special intervention group among smokers, leaving a residual effect that was not statistically robustly different from null. Thus, the increased antihypertensive drug use consequent on the MRFIT intervention may have mitigated against the beneficial effects of other components of the intervention program. Quitting smoking is followed by weight gain (or less weight loss), which is a powerful predictor of diabetes incidence. However, BMI change only explained part of the increased risk for diabetes associated with smoking cessation in both the special intervention and usual care groups, and adjustment for BMI change, which was small in both the special interven-

tion and usual care groups, had little effect on the special intervention–usual care hazard ratio for diabetes among smokers. The greater effect of cessation than BMI change on risk for diabetes could result from our inability to adjust for both BMI changes and changes in central fat distribution. Studies have shown that waist circumference and waist-to-hip ratio (neither was measured in the MRFIT) are more important predictors of diabetes than BMI (51, 52). The risk factor profile of smokers randomly assigned in the MRFIT places them at an increased risk for diabetes compared with the general population and therefore, among this high-risk group, increases in both weight and waist-to-hip ratio are likely to have led to a relative worsening of glucose tolerance and the development of diabetes. Our results do not mitigate against the importance of smoking cessation; rather, they illustrate the necessity to attempt to instigate weight control activities after smoking cessation.

From the University of Bristol, Bristol, United Kingdom; Minneapolis Medical Research Foundation and University of Minnesota, Minneapolis, Minnesota; The University of Texas Health Science Center at San Antonio, San Antonio, Texas; and the University of Pittsburgh, Pittsburgh, Pennsylvania.

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Requests for Single Reprints: George Davey Smith, DSc, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, United Kingdom; e-mail, zetkin@bristol.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Davey Smith: Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, United Kingdom.

Ms. Bracha: Berman Center for Outcomes and Clinical Research, Minneapolis Medical Research Foundation, 825 South Eighth Street, Suite 440, Minneapolis, MN 55404.

Mr. Svendsen and Dr. Neaton: Coordinating Centers for Biometric Research, Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN 55455.

Dr. Haffner: Division of Clinical Epidemiology, Department of Medicine, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7873.

Dr. Kuller: The Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261.

Author Contributions: Conception and design: G. Davey Smith, Y. Bracha, J.D. Neaton.

Analysis and interpretation of the data: G. Davey Smith, Y. Bracha, K.H. Svendsen, J.D. Neaton, L.H. Kuller.

Drafting of the article: G. Davey Smith, Y. Bracha, J.D. Neaton.

Critical revision of the article for important intellectual content: G. Davey Smith, K.H. Svendsen, J.D. Neaton, L.H. Kuller.

Final approval of the article: G. Davey Smith, Y. Bracha, J.D. Neaton, L.H. Kuller.

Statistical expertise: Y. Bracha, K.H. Svendsen, J.D. Neaton.

Obtaining of funding: J.D. Neaton.

Collection and assembly of data: J.D. Neaton.

Appendix Table 1. Risk Factor Levels at Baseline according to Baseline Smoking Status for Multiple Risk Factor Intervention Trial Participants*

Baseline Risk Factor	Nonsmokers	Smokers	P Value
Systolic blood pressure, mm Hg	138.6	133.0	<0.0001
Diastolic blood pressure, mm Hg	93.5	88.9	<0.0001
Pulse, beats/min	75.9	77.7	<0.0001
Antihypertensive treatment, %	24.5	16.0	<0.0001
Total cholesterol level, mmol/L (mg/dL)	6.4 (247.6)	6.1 (235.9)	<0.0001
HDL cholesterol level, mmol/L (mg/dL)	1.1 (43.7)	1.0 (41.4)	<0.0001
Thiocyanate level, mEq/L	65.3	167.7	<0.0001
Leukocyte count, $\times 10^9$ cells/L	6.1	7.8	<0.0001
Weight, lb	191.3	187.5	<0.0001
BMI, kg/m ²	28.2	27.3	<0.0001
Fasting glucose level, mmol/L (mg/dL)	5.5 (99.1)	5.4 (96.5)	<0.0001
Total fat, % kcal	37.3	38.2	<0.0001
Saturated	13.3	14.0	<0.0001
Polyunsaturated	6.5	6.1	<0.0001
Dietary cholesterol, mg/1000 kcal	159.3	166.8	0.0006
Protein, % kcal	16.5	15.9	<0.0001
Total carbohydrates, % kcal	40.9	38.9	<0.0001
Drinks per wk, n	10.5	13.7	<0.0001

* BMI = body mass index; HDL = high-density lipoprotein.

Appendix Table 2. Risk Factor Levels after 6 Years of Follow-up according to Baseline Smoking Status and Treatment Group for Multiple Risk Factor Intervention Trial Participants

Risk Factor Status at Year 6	Nonsmokers			Smokers			P Value for Interaction
	Special Intervention Group	Usual Care Group	P Value	Special Intervention Group	Usual Care Group	P Value	
Systolic blood pressure, mm Hg	121.7	128.4	<0.0001	121.0	125.4	<0.0001	<0.0001
Diastolic blood pressure, mm Hg	81.2	85.2	<0.0001	80.0	82.7	<0.0001	<0.0001
Pulse, beats/min	69.0	70.0	<0.0001	72.2	73.6	<0.0001	0.91
Antihypertensive treatment, %	67.9	55.6	<0.001	51.5	40.9	<0.0001	0.26
Total cholesterol level, mmol/L (mg/dL)	6.1 (233.9)	6.3 (241.5)	<0.0001	5.8 (224.6)	5.9 (228.1)	<0.0001	<0.0001
HDL cholesterol level, mmol/L (mg/dL)	1.1 (42.6)	1.1 (43.1)	0.24	1.1 (41.3)	1.1 (41.3)	>0.2	0.26
Quit smoking, %	–	–	–	49.1	29.0	<0.0001	–
Thiocyanate level, mEq/L	60.1	62.4	0.017	126.9	143.1	<0.0001	<0.0001
Leukocyte count, $\times 10^9$ cells/L	6.1	6.2	0.12	7.2	7.5	<0.0001	0.037
Weight, lb	186.7	191.1	<0.0001	189.0	189.3	0.0041	<0.0001
BMI, kg/m ²	27.5	28.1	<0.001	27.5	27.6	0.0046	<0.0001
Total fat, % kcal	32.3	36.7	<0.0001	34.6	38.2	<0.0001	0.020
Saturated	9.3	12.8	<0.0001	10.8	13.6	<0.0001	0.0002
Polyunsaturated	8.5	6.7	<0.0001	8.0	6.6	<0.0001	0.013
Dietary cholesterol, mg/1000 kcal	115.1	160.8	<0.0001	136.9	173.2	<0.0001	0.017
Protein, % kcal	17.2	16.9	0.091	17.0	16.3	<0.0001	0.046
Total carbohydrates, % kcal	46.9	42.6	<0.0001	42.7	40.0	<0.0001	<0.0001
Drinks per wk, n	7.9	8.2	0.16	10.6	11.9	<0.0001	0.054
Physical activity > peer level, %	42.0	39.2	0.075	32.3	29.2	0.0067	0.70

* BMI = body mass index; HDL = high-density lipoprotein.