Published in final edited form as:

Am J Med. 2009 April ; 122(4): 374–379. doi:10.1016/j.amjmed.2008.09.044.

Aspirin use and risk of type 2 diabetes in apparently healthy men

Yasuaki Hayashino, MD, DMSc, MPH¹, Charles H. Hennekens, MD, DrPH^{2,3}, and Tobias Kurth, MD, ScD^{4,5,6}

¹ Department of Epidemiology and Healthcare Research, Kyoto University Graduate School of Medicine, Kyoto, Japan

² Departments of Medicine & Epidemiology and Public Health, University of Miami School of Medicine, Miami, FL

³ Department of Clinical Science and Medical Education & Center of Excellence, Florida Atlantic University, Boca Raton, FL

⁴ Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

⁵ Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

⁶ Department of Epidemiology, Harvard School of Public Health, Boston, MA

Abstract

Background—Epidemiological data on aspirin use and the risk of diabetes are limited. The Physician's Health Study has accumulated 22 years of follow-up data, including 5 years of randomized data, from 22,071 apparently healthy men.

Methods and results—At baseline and in yearly follow-up questionnaires, participants self-reported a history of diabetes, aspirin use and various lifestyle factors. To evaluate the association between aspirin use and risk of subsequent diabetes, we used a Cox-proportional hazards model with time-varying regression coefficients. During the 22 follow-up years, 1719 cases of diabetes were reported. The multivariable-adjusted hazard ratio (HR) of developing diabetes was 0.86 (95% confidence interval [CI], 0.77–0.97) for those who self-selected any aspirin. During the 5 years of randomized treatment, 318 cases of diabetes were observed, with an HR of 0.91 (95% CI, 0.73–1.14) for those randomized to aspirin.

CORRESPONDENCE TO: Yasuaki Hayashino MD, PhD, MPH, Kyoto University Graduate School of Medicine, Department of Epidemiology and Healthcare Research, Yoshida-konoe-cho, Sakyo-ku, Kyoto 606–8501, Phone: +81-75-753-9467, Fax: +81-75-753–4646, E-mail: hayasino-y@umin.net.

ALL AUTHORS HAD ACCESS TO THE DATA AND A ROLE IN WRITING THE MANUSCRIPT

FULL DISCLOSURE FOR ALL AUTHORS: Dr. Hayashino has nothing to disclose. Dr. Hennekens is funded by the Charles E. Schmidt College of Biomedical Science, Department of Clinical Science and Medical Education & Center of Excellence at Florida Atlantic University (FAU) as Principal Investigator on two investigator-initiated research grants funded to FAU by Bayer testing the effects of aspirin dose on platelet biomarkers, inflammatory markers, nitric oxide formation, and endothelial function; he serves as an independent scientist in an advisory role to investigators and sponsors, including as Chair or Member on Data and Safety Monitoring Boards, for Actelion, Amgen, AstraZeneca, Bayer, Biovail, Bristol-Myers Squibb, Chattem, Dainippon Sumitomo, Delaco, Dechert, Food and Drug Administration, GlaxoSmithKline, Keryx, Lilly, McNeil, Merck, National Association for Continuing Education, National Institutes of Health, Novartis, Pfizer, PriMed, Reliant, Sanofi-Aventis, Sidley Austin, Solvay, TAP, United BioSource Corporation, UpToDate and Wyeth; he serves on speakers bureaus for the International Atherosclerosis Society, AstraZeneca concerning lipids and heart failure, as well as Bristol-Myers Squibb, Reliant and Pfizer concerning lipids; he receives royalties for authorship or editorship of three textbooks; he receives royalties as co-inventor on patents concerning inflammatory markers and cardiovascular disease which are held by Brigham and Women's Hospital; he has an investment management relationship with SunTrust Bank who has sole discretionary investment authority. Dr. Kurth has received within the last 5 years investigator-initiated research funding as Principal or Co-Investigator from the National Institutes of Health, Bayer AG, McNeil Consumer & Specialty Pharmaceuticals, Merck, and Wyeth Consumer Healthcare; he is a consultant to i3 Drug Safety, and received an honorarium from Organon for contributing to an expert panel.

Conclusions—Our data suggest a small but not significant decrease in the risk of diabetes during 5 years of randomized comparison of 325 mg of aspirin every other day. This trend was continued during 22 years of follow-up, indicating that self-selection of any use of aspirin is associated with a significant, approximately 14% decrease in the risk of diabetes. Decreased risk of type 2 diabetes may be added to the list of the clinical benefits of aspirin.

Keywords

aspirin; diabetes; men; cohort study; epidemiology; incidence

INTRODUCTION

Type 2 diabetes mellitus is one of the most prevalent chronic diseases, affecting more than 13.3 million people in the U.S. alone, a number which has doubled over the past 20 years.¹ Diabetes imposes a substantial social and economic burden and is the leading cause of non-traumatic lower extremity amputation, renal failure and blindness in working-age adults, as well as a major cause of mortality through cardiovascular disease, stroke, and peripheral artery disease.² Due to its preventive effect on cardiovascular events, use of aspirin is recommended by the American Diabetes Association and American Heart Association for individuals with type 2 diabetes who have experienced cardiovascular disease or show atherogenic risk factors.³ The association between aspirin and glycemic control, however, is still under investigation. Several earlier clinical studies suggested that aspirin improves insulin sensitivity and glycemic control in patients with type 2 diabetes,^{4–7} whereas three other studies suggested that aspirin impairs insulin sensitivity in healthy volunteers.^{8–10}

A causal association between aspirin and the incidence of diabetes appears biologically plausible due to the suggested partial role of chronic low-grade inflammation in atherosclerosis,¹¹ which possibly shares the same inflammatory basis as diabetes.^{12–14} In recent studies in rodents, high-dose aspirin was shown to reverse hyperglycemia, hyperinsulinemia and dyslipidemia in obese rodents, as well as lower blood glucose concentration by inhibiting the I κ B kinase- β (IKK- β) pathway, which is not inhibited by other non-steroidal anti-inflammatory drugs (NSAIDs)^{15, 16}. Despite these findings, analytic studies on aspirin or non-aspirin NSAIDs and the risk of diabetes in free-living human populations are limited.

We thus investigated the relationship between aspirin or non-aspirin NSAIDs and the subsequent risk of type 2 diabetes mellitus. Analysis was carried out using randomized data from the Physicians' Health Study, which included 22,071 apparently healthy male physicians treated with 325 mg aspirin every two days for five years, followed by analysis of prospective observational data, in which a variety of doses were self-selected for an additional 17 years.

METHODS

Study Population

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial designed to test the risk and benefits of low-dose aspirin and beta carotene assignment on the risk of cardiovascular disease and cancer in apparently healthy men.^{17,18} A detailed description of the subjects and methods has been previously published.^{17–19} Briefly, 22,071 male physicians, aged 40 to 84 years at baseline in 1982, who were free of cardiovascular disease, cancer, or other major disease and had no indication or contraindications to aspirin treatment were administered a 325-mg tablet of aspirin or 50-mg capsule of β -carotene every other day along with a corresponding aspirin or β -carotene placebo, both active agents, or both placebos at random using a 2×2 factorial design.

In January 25, 1988, the randomized aspirin component of the study was prematurely terminated based on the unanimous recommendation of the external data monitoring board, primarily due to the emergence of a statistically extreme 44% reduction in risk of first myocardial infarction after aspirin administration.¹⁷ Following this termination, physicians were allowed to request an aspirin pill replacement containing active aspirin instead of placebo. The randomized β -carotene component of the study continued uninterrupted until its scheduled termination, on December 31, 1995, which was followed by post-trial experimental follow-up.²⁰

A total of 638 men who reported having diabetes before participating in the study were excluded from the analysis.

Questionnaires

Information on height and weight, previously diagnosed medical conditions, including diabetes mellitus, hypertension history, high cholesterol levels, parental history of myocardial infarction, as well as lifestyle factors, such as cigarette smoking (never, past, currently smoking), frequency of alcohol intake (“daily (≥ 1 drink per day)”, “weekly (1–6 drinks per week)”, “monthly (1–3 drink per month)”, “rarely or never drink”) and frequency of vigorous exercise, was collected at baseline by mailed questionnaires.

Every six months for the first year and annually thereafter, participants were mailed follow-up questionnaires inquiring about compliance with the randomized treatment, non-study use of aspirin and non-aspirin NSAIDs, as well as any new medical diagnosis, particularly diabetes. Given the age structure of the population sample, all incident cases of diabetes were diagnosed after age 40 years and classified as type 2 diabetes mellitus. The vital status of all physicians was also known.

Assessment of Aspirin and NSAID Use

During the randomized and post-trial observational period, participants completed annual questionnaires inquiring about compliance with study medication, as well as outside use of aspirin and non-aspirin NSAIDs. This information was used to consistently group subjects by aspirin or NSAID use, in terms of no use (0 days), 1 to 60 days of use, and more than 60 days of use. Details of this categorization have been comprehensively described elsewhere.²¹

Statistical Analysis

The association of aspirin and NSAID use with diabetes incidence was evaluated using Cox-proportional hazards models with time-varying exposure information. Person-time was calculated from the date of randomization to that of diabetes, death, or receipt of the last questionnaire, whichever occurred first.

First, we investigated the association between randomized aspirin assignment and the risk of diabetes on an intention-to-treat basis until the end of the aspirin arm of the trial. Next, we investigated the association between self-selection of aspirin (0 day/year or any use of aspirin) and risk of diabetes by multivariable-adjusted model analyses based on data from the combined aspirin categories, which were collected from randomization until the end of the 22-year follow-up period. We also performed the analysis by stratifying aspirin dose (0 day/year vs. 1–60 days/year or >60 days/year) using age- and multivariable-adjusted models. In addition, the association between non-aspirin NSAIDs and diabetes was analyzed by calculating age- and multivariable-adjusted hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). The multivariable models controlled for variables considered potential confounders, namely age (in five-year increments); body mass index (<25, 25–29.9, ≥ 30); smoking history (never, past, currently smoking); history of hypertension (self-reported

systolic blood pressure ≥ 140 mmHg, diastolic pressure ≥ 90 mmHg or use of antihypertensive medication); history of hypercholesterolemia (serum cholesterol ≥ 240 mg/dl or use of cholesterol-lowering medication); history of hypercholesterolemia (serum cholesterol ≥ 240 mg/dl or use of cholesterol-lowering medication); parental history of myocardial infarction before age 60 years; alcohol use (daily, weekly, monthly, rarely or never); and exercise. Linear trends were analyzed across aspirin and NSAID intake categories. To evaluate the rational of treating study and non-study use of aspirin as having the same effect, the interaction of study and non-study use on the risk of diabetes was evaluated using indicator variables for each aspirin category combination. Further, we evaluated the effect modification of the association between aspirin use and diabetes by age (<60 or ≥ 60), obesity (BMI <30 or ≥ 30), smoking (currently smoking or not) or hypertension history. Statistical interactions between study and non-study use of aspirin, or interactions between combined aspirin use and smoking and hypertension risk factors were analyzed using likelihood ratio tests, which compared the -2 log (likelihood) between two nested models: one considering the main effects alone, and the second the main effects and additional interaction terms. All analyses were conducted using SAS, version 8.2 (SAS Institute, Cary, NC).

RESULTS

During the 5 years of randomized aspirin treatment (105,625 person years), 318 incident cases of diabetes were reported. In contrast, 1719 cases were reported during the 22 years from randomization until the end of the follow-up period, during which participants self-selected a variety of aspirin doses. The age-adjusted baseline characteristics with respect to diabetes incidence after study enrollment are summarized in Table 1. Participants who developed diabetes during the follow-up period were more likely to be obese, hypertensive, have high cholesterol, and report a parental history of myocardial infarction. Further, they were more likely to be current smokers and less physically active, and to drink less alcohol.

Table 2 shows the number of person-years in each combined aspirin category for the 60-month interval subsequent to aspirin use. Because participants were not allowed to use additional aspirin at baseline, fewer person-years were spent in the 1–60 days of aspirin use/year category than in the 0 and >60 days/year categories between baseline and the 60-month follow-up period. In addition, participants were more likely to frequently use aspirin as the study progressed; between 120 months and 180 months, results show 63,812 person-years in the >60 days/year category, whereas 10,904 person-years were not classified in any category.

During the five years of randomized treatment, intention-to-treat analysis revealed a hazard ratio (HR) for diabetes development of 0.91 for the aspirin group (95% confidence interval (CI), 0.73–1.14) compared to the aspirin placebo group. Observational comparisons over 22 years showed a multivariable-adjusted HR for diabetes of 0.86 (95% CI, 0.77–0.97) for subjects who self-selected any aspirin. Further, stratification by aspirin dose revealed that compared to non-aspirin users, multivariable-adjusted HRs for diabetes in men who used aspirin for 1–60 and >60 days/year were 0.83 (95% CI, 0.71–0.98) and 0.87 (95% CI, 0.78–0.98), respectively (Table 3). The likelihood ratio test showed no significant interaction between study and additional aspirin use in reducing the risk of type 2 diabetes. Contrary to the aspirin findings, we did not observe a decrease in risk of developing diabetes by non-aspirin NSAIDs: compared with subjects who did not use non-aspirin NSAIDs, the age-adjusted HRs for diabetes in men who used non-aspirin NSAIDs for 1–60 and >60 days/year were 0.97 (95% CI, 0.87–1.08) and 1.11 (95% CI, 0.93–1.32), respectively. This association remained non-significant after adjustment for a large number of confounders, including age, body mass index, history of smoking, hypertension, high cholesterol, parental myocardial infarction before age 60 years, alcohol use, and exercise.

To examine the possible effect modification of the association between aspirin and diabetes incidence based on diabetes risk factors for which an association with inflammation has been reported, a stratified analyses by these risk factors were was performed (Table 4). Results showed no statistically significant effect modification by hypertension, BMI, smoking status, or age at randomization.

DISCUSSION

Results from randomized comparisons over 5 years suggest a small but non-significant reduction in the risk of diabetes after administration of 325 mg aspirin on alternate days. This trend continued during 22 years of observational follow-up, indicating a significant, approximately 14% reduction in relative risk, which remained significant after adjustment for a large number of potential confounders. We observed no beneficial association between the use of non-aspirin NSAIDs and risk of diabetes.

Our findings are consistent with those from a number of previous clinical studies which evaluated the association between salicylates and glycemic control. In 1877 and 1902, Ebstein and Williamson et al.,^{4, 5} respectively, showed that high-dose salicylate treatment reduced the severity of glycosuria in diabetic patients. In 1957, Reid et al. also observed a decrease in glycosuria and blood sugar in a diabetic patient treated with aspirin for acute rheumatism,⁶ and further demonstrated an improvement in test results for the oral glucose tolerance in diabetic patients after 10–14 days of aspirin treatment.^{6, 22} A randomized trial in type 2 diabetic patients treated for two weeks with high-dose aspirin reported a significant decrease in hepatic glucose production, fasting plasma glucose, fatty acids, and triglycerides.⁷

Our findings, which show that aspirin, but not non-aspirin NSAIDs, reduce the risk of developing diabetes, are also consistent with plausible biological mechanisms. A recent finding suggests that salicylates inhibit inflammation through a pathway different from cyclooxygenase inhibition. Salicylate affects a key pathway in tissue inflammation by inhibiting nuclear factor κ B (NF κ B) and its upstream activator, I κ B kinase- β (IKK- β),²³ which is activated by inflammatory mediators (e.g., TNF- α , IL-1 β), high glucose, and obesity.^{15, 24, 25} Further, activated IKK- β induces the synthesis of TNF- α and IL-1 β , resulting in a cycle which induces insulin resistance and perpetual TNF- α production initiation. This pathway, however, is not associated with non-aspirin NSAIDs.²³ Our negative result for non-aspirin NSAIDs may indirectly suggest that the cyclooxygenase-mediated inflammatory pathway does not play an important role in the development of type 2 diabetes.

To date, randomized controlled trials have demonstrated the efficacy of three types of medication in the prevention or delay of type 2 diabetes^{26–28}. These trials were conducted in subjects with impaired glucose tolerance who were consequently a high-risk population for diabetes incidence. The DPP, STOP-IDDM and TRIPOD studies showed a 31%, 32%, and 56% decrease in diabetes risk using biguanide metformin, the α -glucosidase inhibitor acarbose, and the thiazolidinedione troglitazone, respectively^{26–28}. The American Diabetes Association does not recommend the use of these drugs for the prevention of type 2 diabetes, however, due to their required monitoring, association with significant adverse side effects, and contraindication in a few individuals, as well as the absence of studies on these drugs showing an effect on coronary vascular diseases or other clinical benefits to nondiabetic individuals. Although the reduction in diabetes risk by aspirin should be carefully evaluated, its use is potentially valuable in the prevention of this condition owing to its beneficial effect in even non-diabetic populations if they have high risk of coronary artery disease, and is already recommended by the U.S. Preventive Services Task Force (USPSTF). Aspirin is also currently used in nondiabetic populations for the prevention of coronary vascular disease.²⁹

The strengths of our study include its prospective design, large number of outcome events and high participant follow-up rate, detailed assessment of aspirin and NSAIDs, as well as use of physicians as study subjects, which may have reduced confounding caused by variability in medical care access, as well as educational and socioeconomic status. In addition, we controlled for a large number of potential confounding factors. Upon enrollment in the Physicians' Health Study, participants had no indication or contraindication for aspirin or NSAID use, which have reduced any residual confounding by prior use.

Several limitations of the study also warrant mention. First, our cohort was not screened at baseline for glucose tolerance, fasting glucose, or HbA1c. Further, the clinical diagnosis of diabetes was self-reported, resulting in possible underdiagnosis of type 2 diabetes cases.³⁰ However, underdiagnosis of diabetes would be expected to be lower among physicians than in the general population. Furthermore, such non-differential misclassification would likely lead to an underestimation of effect. Second, only data on the number of days of aspirin or NSAIDs use was available, as opposed to data on actual drug dose. Further, the absence of variation in the association of aspirin dosage and risk of diabetes is possibly due to misclassification bias, or alternatively to residual and uncontrollable confounding, despite controlling for a large number of potential confounding factors. Third, participants in the Physicians' Health Study were predominantly Caucasians. Nevertheless, based on current knowledge, differential biological effects of aspirin and NSAIDs on diabetes among different populations appear unlikely.

In summary, our data suggest a small but not significant decrease in the risk of diabetes during 5 years of a randomized comparison of 325 mg of aspirin every other day. This trend was continued during 22 years of follow-up, indicating that self-selection of aspirin is associated with a significant, approximately 14% decrease in the risk of diabetes. Decreased risk of type 2 diabetes may be added to the list of clinical benefits of aspirin. Future studies are warranted to further investigate this association.

Acknowledgements

We are indebted to the participants in the Physicians' Health Study for their outstanding commitment and cooperation, to the entire Physicians' Health Study staff for their expert and unfailing assistance, and to Eunjung Kim for programming assistance.

FUNDING SOURCES: The Physicians Health Study was supported by grants CA-34944, CA-40360, and CA-097193 from the National Cancer Institute and grants HL-26490 and HL-34595 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. The study sponsors were not involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; nor the preparation, review, or approval of the manuscript.

References

1. Nilsson PM, Roost M, Engstrom G, Hedblad B, Berglund G. Incidence of diabetes in middle-aged men is related to sleep disturbances. *Diabetes Care* 2004;27(10):2464–9. [PubMed: 15451917]
2. Type 2 Diabetes Complications. 2004 [Accessed 22, December, 2004]. at <http://www.diabetes.org/type-2-diabetes/complications.jsp>
3. Colwell JA. Aspirin therapy in diabetes. *Diabetes Care* 2004;27(Suppl 1):S72–3. [PubMed: 14693931]
4. Ebstein W. Zur therapie des diabetes mellitus insbesondere uber die anwedung des salicylsuren natron bei demselben. *Berl Klin Wochenschr* 1876;13:337–40.
5. Williamson RT, Loud MD. On the treatment of glycosuria and diabetes mellitus with sodium salicylate. *Br Med J* 1901;1:760.
6. Reid JAIM, Andrews MM. Aspirin and diabetes mellitus. *Br Med J* 1957;2:1071. [PubMed: 13472052]
7. Hundal RS, Petersen KF, Mayerson AB, et al. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. *J Clin Invest* 2002;109(10):1321–6. [PubMed: 12021247]

8. Bratusch-Marrain PR, Vierhapper H, Komjati M, Waldhausl WK. Acetyl-salicylic acid impairs insulin-mediated glucose utilization and reduces insulin clearance in healthy and non-insulin-dependent diabetic man. *Diabetologia* 1985;28(9):671–6. [PubMed: 3905478]
9. Giugliano D, Sacca L, Scognamiglio G, Ungaro B, Torella R. Influence of acetylsalicylic acid on glucose turnover in normal man. *Diabete Metab* 1982;8(4):279–82. [PubMed: 6819169]
10. Newman WP, Brodows RG. Aspirin causes tissue insensitivity to insulin in normal man. *J Clin Endocrinol Metab* 1983;57(6):1102–6. [PubMed: 6355137]
11. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336(14):973–9. [PubMed: 9077376]
12. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *Bmj* 2000;321(7255):199–204. [PubMed: 10903648]
13. Pradhan AD, Ridker PM. Do atherosclerosis and type 2 diabetes share a common inflammatory basis? *Eur Heart J* 2002;23(11):831–4. [PubMed: 12042000]
14. Helmersson J, Vessby B, Larsson A, Basu S. Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. *Circulation* 2004;109(14):1729–34. [PubMed: 15037525]
15. Yuan M, Konstantopoulos N, Lee J, et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. *Science* 2001;293(5535):1673–7. [PubMed: 11533494]
16. Ismail N, Neyra R, Hakim R. The medical and economical advantages of early referral of chronic renal failure patients to renal specialists. *Nephrol Dial Transplant* 1998;13(2):246–50. [PubMed: 9509429]
17. Findings from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1988;318(4):262–4. [PubMed: 3275899]
18. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321(3):129–35. [PubMed: 2664509]
19. Manson JE, Buring JE, Satterfield S, Hennekens CH. Baseline characteristics of participants in the Physicians' Health Study: a randomized trial of aspirin and beta-carotene in U.S. physicians. *Am J Prev Med* 1991;7(3):150–4. [PubMed: 1931143]
20. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334(18):1145–9. [PubMed: 8602179]
21. Sturmer T, Buring JE, Lee IM, Kurth T, Gaziano JM, Glynn RJ. Colorectal cancer after start of nonsteroidal anti-inflammatory drug use. *Am J Med* 2006;119(6):494–502. [PubMed: 16750963]
22. Gilgore SG. The influence of salicylate on hyperglycemia. *Diabetes* 1960;9:392.
23. Yin MJ, Yamamoto Y, Gaynor RB. The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. *Nature* 1998;396(6706):77–80. [PubMed: 9817203]
24. Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science* 1994;265(5174):956–9. [PubMed: 8052854]
25. Maedler K, Sergeev P, Ris F, et al. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002;110(6):851–60. [PubMed: 12235117]
26. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346(6):393–403. [PubMed: 11832527]
27. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359(9323):2072–7. [PubMed: 12086760]
28. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002;51(9):2796–803. [PubMed: 12196473]
29. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136(2):157–60. [PubMed: 11790071]

30. Harris, MI. National Diabetes Data Group: Diabetes in America: USDHHS, NIH; 1985. Report No.: pub no 85-1468. Prevalence of noninsulin-dependent diabetes and impaired glucose tolerance.

Table 1

Age-adjusted Baseline Characteristics of Participants According to Diabetes*

	Diabetes (n=1,719)	No diabetes (n=19,714)
Age (SD)	54.1 (8.7)	53.5(9.5)
Body Mass Index, %		
<25	32.9	60.1
25–29.9	52.9	36.7
≥30	14.2	3.2
Hypertension, % [†]	36.0	21.9
High cholesterol, % [§]	14.9	11.5
Parental history of myocardial infarction before age 60, %	11.1	9.2
Smoking, %		
Never	43.9	50.2
Past	40.3	39.2
Currently smoking	15.8	10.6
Physical activity, % [¶]		
< 1 time/week	36.0	26.6
≥ 1 time/week	64.0	73.4
Alcohol, %		
Daily	19.8	25.4
Weekly	47.6	49.6
Monthly	14.5	10.7
Rarely or never drink	18.2	14.3

* Adjusted for age at baseline (five-year increments)

[†] Defined as reported systolic pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg, or history of treatment for high blood pressure.[§] Defined as reported blood cholesterol level of 240 mg/dl or greater, or history of treatment using cholesterol-lowering medication.[¶] Defined as physical activity of sufficient duration to induce sweating.

Table 2
Aspirin Use and Subsequent Diabetes Mellitus during Follow-up Periods

Follow-up periods	0 day/year			1-60 days/year			>60 days/year			Cumulative deceased
	PY*	DM†	Incidence rate‡ (95% CI)	PY*	DM†	Incidence rate‡ (95% CI)	PY*	DM†	Incidence rate‡ (95% CI)	
Baseline-60 mo	37825	133	3.5 (2.9-4.2)	17802	53	3.0 (2.2-3.9)	49649	141	2.8 (2.4-3.3)	408
61 mo-120 mo	17186	70	4.1 (3.2-5.1)	16501	49	3.0 (2.2-3.9)	65014	246	3.8 (3.3-4.3)	822
121 mo-180 mo	10904	58	5.3 (4.0-6.9)	9893	50	5.1(3.8-6.7)	63812	336	5.3 (4.7-5.9)	1254
181 mo-	19540	117	6.0 (5.0-7.2)	16767	70	4.2 (3.3-5.3)	65135	318	4.9 (4.4-5.4)	2207

* PY indicates person-years in the following time interval listed in this table.

† DM indicates diabetes mellitus cases in the following time interval listed in this table.

‡ Incidence rate of diabetes per 1000 person-years

Table 3
Hazard Ratios (HRs) and 95% CIs According to Time-varying Combined Aspirin and Non-aspirin NSAID Use

	DM, n	Age-adjusted [*] HR (95% CI)	Multivariable-adjusted [†] HR (95% CI)
Combined Aspirin			
None	456	1.00	1.00
1–60 days/year	222	0.79 (0.67–0.93)	0.83 (0.71–0.98)
>60 days/year	1041	0.85 (0.76–0.95)	0.87 (0.78–0.98)
P for trend		0.0049	0.0329
Non-aspirin NSAIDs			
None	1039	1.00	1.00
1–60 days/year	536	0.97 (0.87–1.08)	0.95 (0.85–1.06)
>60 days/year	144	1.11 (0.93–1.32)	0.99 (0.83–1.18)
P for trend		0.3429	0.6552

* Adjusted for age at baseline (five-year increments).

[†] Adjusted for age, BMI, history of hypertension, high cholesterol, smoking, and parental history of myocardial infarction, alcohol use, physical activity

Table 4

Multivariable-adjusted Hazard Ratios (HRs) and 95% CIs According to Combined Aspirin Categories *

	Combined Aspirin Categories			p for interaction
	0	1–60	>60	
Age				0.58
< 60 years	1.00	0.78 (0.65–0.94)	0.83 (0.73–0.95)	
≥60 years	1.00	0.98 (0.69–1.40)	0.96 (0.76–1.21)	
Obesity				0.46
BMI < 30	1.00	0.83 (0.69–0.99)	0.85 (0.75–0.96)	
BMI ≥30	1.00	0.82 (0.52–1.32)	1.03 (0.75–1.42)	
Smoking				0.06
Never or past	1.00	0.77 (0.65–0.93)	0.83 (0.73–0.94)	
Currently smoking	1.00	1.22 (0.82–1.83)	1.19 (0.88–1.62)	
Hypertension [†]				0.09
No	1.00	0.71 (0.58–0.88)	0.79 (0.69–0.92)	
Yes	1.00	1.12 (0.85–1.48)	1.04 (0.85–1.26)	

* Adjusted for all variables in the multivariable-adjusted model in Table 3.

[†] Defined as reported systolic pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg, or history of treatment for high blood pressure.