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Menopause and risk of diabetes in the Diabetes Prevention Program

Catherine Kim, M.D., M.P.H.,

Departments of Medicine and Obstetrics & Gynecology, University of Michigan, Ann Arbor, MI

Sharon L. Edelstein, Sc.M.,

The Biostatistics Center, George Washington University, Rockville, M.D

Jill P. Crandall, M.D.,

Departments of Medicine, Albert Einstein College of Medicine, New York, N.Y

Dana Dabelea, M.D., Ph.D.,

Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Denver, CO

Abbas E. Kitabchi, Ph.D., M.D.,

Department of Medicine, University of Tennessee, Memphis, TN

Richard F. Hamman, M.D., Dr.Ph.,

Department of Epidemiology, University of Colorado, Denver, CO

Maria G. Montez, R.N., M.S.H.P.,

Department of Medicine, University of Texas Health Sciences Center, San Antonio, TX

Leigh Perreault, M.D.,

Department of Medicine, University of Colorado, Denver, CO

Mary A. Foulkes, Ph.D., and

Department of Epidemiology and Biostatistics, George Washington University, Rockville, M.D

Elizabeth Barrett-Connor, M.D.

Department of Family Medicine, University of California, La Jolla, CA

for the Diabetes Prevention Program Research Group

Abstract

Objective—The study objective was to examine the association between menopause status and diabetes risk among women with glucose intolerance and to determine if menopausal status modifies response to diabetes prevention interventions.

Methods—The study population included women in premenopause (n=708), natural postmenopause (n=328), and bilateral oophorectomy (n=201) in the Diabetes Prevention Program (DPP), a randomized placebo-controlled trial of lifestyle intervention and metformin among glucose intolerant adults. Associations between menopause and diabetes risk were evaluated using Cox proportional hazard models that adjusted for demographic variables (age, race/ethnicity, family history of diabetes, history of gestational diabetes mellitus), waist circumference, insulin

resistance and corrected insulin response. Similar models were constructed after stratification by menopause type and hormone therapy (HT) use.

Results—After adjustment for age, there was no association between natural menopause or bilateral oophorectomy and diabetes risk. Differences by study arm were observed in women who reported bilateral oophorectomy. In the lifestyle arm, women with bilateral oophorectomy had a lower adjusted hazard for diabetes (HR 0.19, 95% CI 0.04, 0.94), although observations were too few to determine if this was independent of HT use. No significant differences were seen in the metformin (HR 1.29, 95% CI 0.63, 2.64) or placebo arms (HR 1.37, 95% CI 0.74, 2.55).

Conclusions—Among women at high-risk for diabetes, natural menopause was not associated with diabetes risk and did not affect response to diabetes prevention interventions. In the lifestyle intervention, bilateral oophorectomy was associated with decreased diabetes risk.

MeSH keywords

diabetes; impaired glucose tolerance; menopause; oophorectomy; women

Several types of evidence suggest that menopause could be associated with more rapid progression of glucose intolerance. First, postmenopause may be a relatively androgenic state compared to premenopause due to cessation of ovarian estrogen production and continuation of androgen production.¹ Second, greater levels of endogenous androgens are associated with glucose intolerance in both premenopausal and postmenopausal women.² Third, postmenopausal estrogen therapy reduces fasting plasma glucose (FPG) levels.³

It is unknown if menopause per se is associated with higher glucose levels, particularly among women who are already glucose intolerant. As diabetes is typically defined by glucose levels, the presence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are strong risk factors for diabetes, and the menopausal state may not have any additional effect. While several longitudinal studies have found no association between menopause and glucose,^{4–6} these studies did not measure the associations between menopause and key mediators of glucose tolerance, specifically insulin secretion and insulin resistance, or other biomarkers. Furthermore, these studies did not compare diabetes risk among the population of women with bilateral oophorectomy as opposed to natural menopause. Bilateral oophorectomy reduces testosterone levels⁷ and high testosterone is a risk factor for diabetes in women.² Finally, it is also unknown if diabetes prevention interventions are more effective in premenopausal compared to postmenopausal women.

If menopause status is a risk factor for diabetes among women who are already high-risk, or modifies response to diabetes prevention interventions, this has implications for targeted diabetes prevention interventions. The Diabetes Prevention Program (DPP) was a randomized trial of diabetes prevention interventions among adults with IFG and IGT. Using data from the DPP, we examined diabetes risk associated with menopause status, comparing women who were premenopausal with women who were postmenopausal at baseline. We also examined if menopause status modified the effect of DPP interventions on a number of metabolic variables, including adiposity, insulin metabolism, glucose, adiponectin, C-reactive protein (CRP), fibrinogen, and tissue plasminogen activator antigen (tPA). Finally, we examined whether the associations between natural menopause and diabetes risk differed from those of bilateral oophorectomy and diabetes risk before and after consideration of hormone therapy (HT).

Methods

Characteristics of DPP participants have been reported.⁸ Briefly, the DPP inclusion criteria included age ≥ 25 years, an FPG of 5.3–6.9 mmol/l or 95–124 mg/dl (≥ 6.9 mmol/l in the Native American centers) and a 2-hour plasma glucose of 7.8–11.1 mmol/l or 140–200 mg/dl following a 75-g glucose load, age ≥ 25 years, and BMI ≥ 24 kg/m² (≥ 22 kg/m² for Asian Americans). Written informed consent was obtained from all participants before screening, consistent with the guidelines of each center's institutional review board.

Eligible participants recruited between 1996 and 1999 were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily, or intensive lifestyle. The goals of the lifestyle intervention were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet, and to engage in moderate physical activity for at least 150 min/week.⁸ Diabetes was diagnosed on the basis of an annual oral glucose tolerance test (OGTT) or a semiannual FPG test.⁹ The diagnosis required confirmation by a second test, usually within 6 weeks. At the time of randomization, all women completed a questionnaire about their menses, gynecological history including surgeries, current oral contraceptive (OCP) and HT use. Menstrual bleeding pattern in the previous year was not assessed beyond baseline, nor was the type of HT or OCP ascertained. Participants were followed for an average of 3.2 years, updated from the 2.8 years reported previously.⁸

For this analysis, we included female DPP participants aged 40–64 years at randomization. The cut-off of 40 years was chosen to exclude “premature” or atypical menopause, typically defined as cessation of menses before the age of 40.¹⁰ The cut-off of 65 was chosen to exclude women who reported continued vaginal bleeding after the age of 65 years as this bleeding was less likely due to menses and more likely to due to pathologic processes; thus, we chose an age range that would include women who could be pre- or post-menopausal. We excluded women who reported irregular menses in the past year, or who initiated HT while menstruating, or who reported menses up to the time of hysterectomy (n=384).

Women reporting current, regular menstruation were classified as being premenopausal (n=708). Women were classified as being postmenopausal at baseline if they reported that at least one year had elapsed since their last menstrual period (n=529). Among postmenopausal women, women were classified as having surgical menopause if they reported bilateral oophorectomy (n=201). Among women who reported not bleeding for at least one year, women were classified as being in natural menopause if they had a uterus and at least part of one ovary, or if they stopped menstruating at least a year before a hysterectomy and had at least part of one ovary (n=328). Other self-reported variables included age, race/ethnicity, family history of diabetes, smoking history, parity, history of gestational diabetes mellitus (GDM), and menopausal status.

Glucose and insulin were measured as previously reported.¹¹ Briefly, women were instructed to consume a usual diet and an OGTT was performed between 7 a.m. and 11 a.m. after an overnight fast. Blood was sampled from a vein before (fasting), and 30 minutes and 2 hours after a 75-gram oral glucose load (Trutol 75; Custom Laboratories, Baltimore, MD). Plasma glucose was measured fasting, at 30 minutes, and 2-hours, and plasma insulin was measured fasting and at 30 minutes. Beta cell function was assessed using the corrected insulin response (CIR) = $(100 \times 30\text{-min insulin}) / (30\text{-min glucose} \times [30\text{-min glucose} - 70 \text{ mg/dl}])$.¹¹ Insulin sensitivity was assessed using inverse fasting insulin levels.¹¹

Total circulating adiponectin was measured at baseline and one year after randomization using a latex particle-enhanced turbidimetric assay (Otsuka Pharmaceutical, Tokyo, Japan). The within-run and total coefficient of variation for this assay are 0.8–1.9% and 1.1–2.0%,

respectively, and results are highly correlated with enzyme-linked immunosorbent assay–based methods ($r = 0.99$).¹² Other analytes were measured at baseline and at one year post-randomization in a central laboratory as previously reported.¹² High-sensitivity CRP and fibrinogen levels in plasma were measured immunochemically using Dade-Behring reagent on the Behring Nephelometer autoanalyzer, which uses polystyrene particles coated with monoclonal antibodies specific to the ligand. The intra- and inter-assay coefficients of variation for CRP were 4 and 5%, respectively. The intra- and inter-assay coefficients of variation for fibrinogen were 3 and 5%, respectively.¹³ TPA was measured in citrated plasma using an enzyme-linked immunosorbent assay (Asserachrom tPA; Diagnostica Stago), which measures total tPA antigen.¹⁴

Baseline characteristics were described using percentages for categorical variables and means (SD) for quantitative variables. Comparisons between premenopausal and postmenopausal women were made using the χ^2 test of independence for categorical variables and the t test for quantitative variables. Cox proportional hazard models were used to assess the association between menopausal status and diabetes risk after adjustment for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, insulin resistance (defined as $1/\text{fasting insulin}$), and CIR.¹¹ Models were constructed for the entire sample; for premenopausal women and women in natural menopause only; for premenopausal women and women with bilateral oophorectomy; for premenopausal women and postmenopausal women not using HT currently; and for premenopausal women and postmenopausal women using HT currently.

To determine if baseline menopause status modified response to interventions, we used a normal errors longitudinal regression model¹⁵ to compare age and baseline adjusted weight, waist circumference, insulin resistance, CIR,¹¹ and glucose levels by menopausal status. We also examined changes in biomarkers including adiponectin, CRP, fibrinogen, and tPA within study arm, and found no differences by menopausal status (results not shown), and we stratified by GDM status but found no differences by menopausal status (results not shown). The SAS analysis system was used for all analyses (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of women by menopausal status and type of menopause are shown in Table 1. Premenopausal women were younger than postmenopausal women, with a mean (SD) age of 45.7 (3.6) years at enrollment; based on previous longitudinal studies,¹⁰ we would estimate that less than 10% of premenopausal women would have naturally transitioned to menopause over the 3-year period. Premenopausal women were also more likely to have a history of GDM and to have ever used OCPs; postmenopausal women were more likely to have ever used HT. While premenopausal women were heavier and had greater waist circumference than women in natural menopause, premenopausal women had similar body habitus to women with bilateral oophorectomy. Compared to women in natural menopause, premenopausal women had lower fibrinogen, adiponectin, and greater tPA. Compared to women with bilateral oophorectomy, premenopausal women had lower CRP and lower adiponectin and tPA.

The unadjusted cumulative incidence of diabetes among premenopausal women was, in cases per 100 person-years, 11.8 in the placebo group, 6.6 in the metformin group, and 6.8 in the lifestyle group. Among postmenopausal women, the unadjusted cumulative incidence of diabetes was, in cases per 100 person-years, 11.5 in the placebo group, 8.9 in the metformin group, and 3.2 in the lifestyle group. Among women in natural postmenopause, the unadjusted cumulative incidence of diabetes was, in cases per 100 person-years, 10.5 in the placebo group, 5.0 in the metformin group, and 4.3 in the lifestyle group. Among women

with bilateral oophorectomy, the unadjusted cumulative incidence of diabetes was, in cases per 100 person-years, 12.9 in the placebo group, 10.3 in the metformin group, and 1.1 in the lifestyle group.

The hazard ratio of diabetes by baseline menopause status before and after adjustment for demographic factors, waist circumference, and CIR and 1/fasting insulin is shown in Table 2. When we examined premenopausal women and postmenopausal women in menopause (natural and bilateral oophorectomy), postmenopausal status was not significantly associated with diabetes risk among women in any randomization arm after adjustment for age. This pattern persisted after further adjustment for other demographic factors including race/ethnicity, family history of diabetes, and history of GDM, and after additional adjustment for waist circumference, insulin resistance and CIR. When we compared premenopausal women to women in **natural** menopause (Table 2), postmenopausal women did not have a greater risk of diabetes overall. While postmenopausal women in the lifestyle arm had a higher risk for diabetes after consideration of multiple risk factors, this risk was not statistically significant. When we compared premenopausal women to women with bilateral oophorectomy (Table 2), we found that postmenopausal women did not have a higher risk of diabetes in any treatment arm. In the lifestyle arm, women who had undergone bilateral oophorectomy had a significantly lower risk for diabetes, i.e. women with bilateral oophorectomy appeared to have a greater benefit from lifestyle intervention as compared to women in premenopause and greater benefit from lifestyle intervention than metformin. This result persisted after adjustment for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, 1/fasting insulin and CIR (Table 2).

Next, we performed these analyses stratified by HT use as well as type of menopause (Table 3). Natural menopause was not associated with greater diabetes risk overall among HT users or non-users. Women in natural menopause who were not using HT had similar diabetes hazard compared to premenopausal women by treatment arm, and women in natural menopause who were using HT also had similar diabetes hazard compared to premenopausal women by treatment arm. Bilateral oophorectomy was also not associated with greater diabetes risk overall among HT users and non-users within treatment arm. In the lifestyle arm, women who had undergone bilateral oophorectomy had a nonsignificantly lower risk for diabetes among HT non-users. However, no HT users with bilateral oophorectomy developed diabetes within the lifestyle arm, and thus we could not determine if bilateral oophorectomy modified response to lifestyle intervention, apart from HT.

To determine whether the impact of interventions on potential mediators was modified by overall menopausal status, we compared changes in weight, waist circumference, 1/fasting insulin, CIR, FPG, and 2-hour glucose levels within study arm, and found no significant differences by menopausal status after adjustment for age (results not shown). Finally, we examined changes in biomarkers including adiponectin, CRP, fibrinogen, and tPA within study arm, and found no differences by menopausal status (results not shown).

DISCUSSION

No previous longitudinal reports have examined the impact of menopause among women who are already at high-risk for diabetes based on glucose levels. In this randomized 3-year trial of interventions for diabetes prevention among women with IFG and IGT, we found that natural menopause was not associated with an increased risk of diabetes. Overall, we found that bilateral oophorectomy was not associated with a decreased risk of diabetes. Bilateral oophorectomy was associated with a decreased risk of diabetes among women randomized to lifestyle intervention, but we could not assess whether this effect was independent of HT.

At the beginning of these analyses, several factors suggested that menopausal status may be associated with higher risk of diabetes in the general population of women: 1) postmenopause may be a relatively androgenic state compared to premenopause due to cessation of ovarian estrogen production and continuation of androgen production by the ovarian stroma,¹ 2) polycystic ovary syndrome (PCOS) is associated with higher androgen levels, and women with PCOS have a greater risk of diabetes than women without PCOS,¹⁶ 3) higher levels of androgens are associated with glucose intolerance in premenopausal and postmenopausal women,² 4) HT is associated with lower FPG values.³ However, the relationship between androgens and glucose has not been consistent. In one cross-sectional study of postmenopausal women (n=29), greater endogenous androgens were actually associated with improved insulin sensitivity.¹⁷ Correction of hyperandrogenemia in women with PCOS has not been associated with a change in insulin sensitivity, suggesting that androgens per se may not change insulin sensitivity in that population, with the caveat being that findings in PCOS women may not extend to the general population of healthy women.¹⁸

For women in natural menopause, there are three potential explanations why the DPP cohort showed no association between menopausal status and diabetes risk. First, all women in the DPP were preselected for IGT at baseline, and menopause may not be a significant risk factor for glucose deterioration among women who are already glucose intolerant. Second, postmenopausal status may not increase diabetes risk. Third, although this analysis included over 1000 women who were premenopausal and in natural menopause, our study may have been underpowered to detect a real, if modest difference after consideration of age.

To our knowledge, no previous longitudinal reports have examined separately diabetes risk in women with bilateral oophorectomy. The SWAN study, which serially examined women as they progressed through menopause, included only premenopausal women and women in natural menopause.⁴ In SWAN, the age-adjusted odds of developing metabolic syndrome (although not diabetes) in perimenopausal women were significantly higher than in postmenopausal women.⁴ In a report by Soriguer and colleagues,⁵ no specification was made regarding surgical vs. natural menopause, and no significant risk of diabetes was found in the postmenopausal population. Finally, in a report from Mishra and colleagues,⁶ no association between menopause status or type of menopause status was found to be associated with diabetes risk. In this paper, surgical menopause was defined as hysterectomy with or without oophorectomy, so that women in “surgical menopause” could have retained both ovaries, which may have led to overlapping hormone profiles between women in “natural” vs. “surgical” menopause.

In our analysis, the decreased diabetes risk associated with bilateral oophorectomy among women enrolled in the lifestyle arm was initially masked by the slight (but non-significant) risk in natural menopause, and this may have occurred in the Soriguer and Mishra analyses as well. In our analysis, among women randomized to the lifestyle arm, women with bilateral oophorectomy had a significantly lower risk of diabetes compared to premenopausal women. Among women randomized to the lifestyle arm, women in natural menopause had a similar risk of diabetes to premenopausal women. Women with bilateral oophorectomy used hormone therapy more often than women in natural menopause (69% vs. 39%, respectively), and tended to have slightly higher weight and greater insulin resistance than women in natural menopause. Therefore, it is possible that the differences in diabetes hazard in the lifestyle arm in women with bilateral oophorectomy and women in natural menopause may have been mediated or confounded by HT use.

Women with bilateral oophorectomy represent a unique population because they have a sudden dramatic decrease in both their androgen and estrogen production. We did not see a significant differential association between natural menopause and diabetes in the DPP

lifestyle group, even as we observed it in the bilateral oophorectomy group. Our findings underscore the potential importance of examining women with bilateral oophorectomy separately from women in natural menopause. While explanations are speculative, the absolute declines in sex hormones and/or relative differences in the balance of these hormones after bilateral oophorectomy may have contributed to a greater benefit of lifestyle intervention among these women, or the more frequent HT use may have also contributed to this greater benefit. In the current report, associations between menopause and diabetes incidence were not altered after consideration of waist circumference in either the overall, bilateral oophorectomy, or natural menopause cohorts. In the parent DPP study, lifestyle intervention was more effective in older age groups.¹⁹

In our report, among women in natural menopause, the similar diabetes incidence after exclusion of HT users and among current HT users further supports the conclusion that HT may not significantly modify diabetes risk among women who are already glucose intolerant. We were unable to assess the impact of HT among women with bilateral oophorectomy in the lifestyle arm, due to the lack of diabetes cases in that arm. We did not ascertain different types of HT, or intermittent use, common in many postmenopausal women, and therefore cannot comment on the associations with diabetes risk between any specific hormone regimen or route of administration. However, at the time the DPP was initiated in 1996, more than 80% of HT use in the United States was oral conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA).²⁰ The epidemiologic literature on HT and diabetes incidence is contradictory. Observational studies are confounded by the fact that women with diabetes are much less likely to be prescribed estrogen²¹ and few studies measured post-challenge glucose.

Among women without known diabetes, one prospective cohort study²² and two randomized clinical trials^{3,23} suggested that oral CEE with continuous MPA decreased diabetes risk, but the diabetes diagnosis was based on self-report without post-challenge glucose, and both trials included women with an intact uterus. In contrast, PEPI, the largest, longest randomized trial to include OGTT as outcome, showed that oral CEE with MPA decreased fasting plasma glucose but also increased 2-hour glucose; results were not reported separately by oophorectomy history.²⁴ Another large trial of unopposed estrogen in women who had a hysterectomy reported a nonsignificant reduced risk of diabetes based on fasting glucose;²⁵ while approximately 40% of that cohort had undergone bilateral oophorectomy, results were not reported separately by oophorectomy history. Clinical trials of HT in women with known diabetes have been small and short, with divergent results and were not able to determine impact among women with bilateral oophorectomy vs. natural menopause.^{26–28}

This paper is unique in its ability to assess a history of menopause and HT as risk factors for diabetes in women with IGT; and in having repeated measures of fasting and post-challenge glycemia; and diabetes diagnoses confirmed by a second glucose assay. However, we also note several limitations. Bilateral oophorectomy was self-reported. Menopause status was not queried after baseline, therefore we could not assess change in menopause status; some premenopausal women whose mean age was 46 at baseline may have transitioned to postmenopause during the 3-year study period. In the SWAN study, more than 80% of women who enrolled at age 42 were still menstruating at 6-year follow-up.¹⁰ Based on SWAN observations, and the fact that premenopausal DPP women had a mean (SD) age of 45.7 (3.6) years at enrollment, we would estimate that less than 10% of premenopausal women would have transitioned to menopause over the 3-year period. The use of OCPs to manage perimenopausal symptoms could have affected premenopausal progression to diabetes but OC use was reported by only 6%. Taken together, these limitations may have biased our results to the null among women in natural menopause. We cannot exclude the

possibility that natural menopause is associated with altered glucose tolerance among women who have normal glucose levels before treatment. We were unable to assess the effects of HT among women in surgical menopause in the lifestyle arm, due to the lack of diabetes cases in that arm. Finally, as in any observational study, there may have been residual confounding by factors such as age.

CONCLUSION

The present report has clinical and public health relevance, showing natural menopause does not modify the impact of diabetes prevention interventions among women at high risk for diabetes. While we did not find a significant association between natural menopause and diabetes risk, our study cannot completely rule out a more modest association. Bilateral oophorectomy may have different effects upon response to lifestyle interventions than natural menopause, but the role of HT needs to be assessed.

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A complete list of centers, investigators, and staff can be found in the Appendix.

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References

1. Sowers M, Derby C, Jannausch M, Torrens J, Pasternak R. Insulin resistance, hemostatic factors, and hormone interactions in pre- and perimenopausal women: SWAN. *J Clin Endocrinol Metab.* 2003; 88:4904–4910. [PubMed: 14557472]
2. Ding E, Song Y, Malik V, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes. *JAMA.* 2006; 295:1288–1299. [PubMed: 16537739]
3. Kanaya A, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/Progestin Replacement Study. *Ann Intern Med.* 2003; 138(1):1–9. [PubMed: 12513038]
4. Janssen I, Powell L, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome. *Arch Intern Med.* 2008; 168(14):1568–1575. [PubMed: 18663170]
5. Soriguer F, Morcillo S, Hernando V, et al. Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause. *Menopause.* 2009; 16(4):817–821. [PubMed: 19387417]
6. Mishra G, Carrigan G, Brown W, Barnett A, Dobson A. Short-term weight change and the incidence of diabetes in mid-life. *Diabetes Care.* 2007; 30:1418–1424. [PubMed: 17351279]

7. Labrie F, Martel C, Balser J. Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: the role of the ovary? *Menopause*. 2010 epub ahead of print(July 28, 2010).
8. Knowler W, Barrett-Connor E, Fowler S, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346:393–403. [PubMed: 11832527]
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2008; 31(Suppl1):S55–60. [PubMed: 18165338]
10. Santoro N, Brockwell S, Johnson J, et al. Helping midlife women predict the onset of final menses: SWAN, the study of Women's Health Across the Nation. *Menopause*. 2007; 14(3):415–424. [PubMed: 17303963]
11. Kitabchi A, Tempresa M, Knowler W, et al. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the Diabetes Prevention Program: effects of lifestyle intervention and metformin. *Diabetes*. 2005; 54(8):2404–2414. [PubMed: 16046308]
12. Mather K, Funahashi T, Matsuzawa Y, et al. Adiponectin, change in adiponectin, and progression to diabetes in the Diabetes Prevention Program. *Diabetes*. 2008; 57(4):980–986. [PubMed: 18192541]
13. Haffner S, Tempresa M, Crandall J, et al. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes*. 2005; 54(5):1566–1572. [PubMed: 15855347]
14. Diabetes Prevention Program Research Group. Lipid, lipoproteins, C-reactive protein, and hemostatic factors at baseline in the Diabetes Prevention Program. *Diabetes Care*. 2005; 28:2472–2479. [PubMed: 16186282]
15. Diggle, P.; Liang, K.; Zeger, S. *Analysis of Longitudinal Data*. New York: Oxford University Press; 1994.
16. Salley K, Wickham E, Cheang K, Essah P, Karjane N, Nestler J. Glucose intolerance in polycystic ovary syndrome--a position statement of the Androgen Excess Society. *J Clin Endocrinol Metab*. 2007; 92(12):4546–4556. [PubMed: 18056778]
17. Casson P, Toth M, Johnson J, Stanczyk F, Casey C, Dixon M. Correlation of serum androgens with anthropometric and metabolic indices in healthy, nonobese postmenopausal women. *J Clin Endocrinol Metab*. 2010; 95(9):4276–4282. [PubMed: 20566621]
18. Lemieux S, Lewis G, Ben-Chetrit A, Steiner G, Greenblatt E. Correction of hyperandrogenemia by laparoscopic ovarian cautery in women with polycystic ovarian syndrome is not accompanied by improved insulin sensitivity or lipid-lipoprotein levels. *J Clin Endocrinol Metab*. 1999; 84:4278–4282. [PubMed: 10566685]
19. Crandall J, Schade D, Ma Y, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci*. 2006; 61(10):1075–1081. [PubMed: 17077202]
20. Stefanick M. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the U.S. Food and Drug Administration. *Am J Med*. 2005; 118(Suppl 12b): 64–73. [PubMed: 16414329]
21. Kanaya A, Grady D, Barrett-Connor D. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus. *Arch Intern Med*. 2002; 162(15):1737–1745. [PubMed: 12153377]
22. Manson J, Rimm E, Colditz G, et al. A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin dependent diabetes mellitus. *Ann Epidemiol*. 1992; 2(5):665–673. [PubMed: 1342318]
23. Margolis K, Bonds D, Rodabough R, et al. Effects of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004; 47(7):1175–1187. [PubMed: 15252707]
24. Espeland M, Hogan P, Fineberg S, et al. Effect of postmenopausal hormone therapy on glucose and insulin concentrations. PEPI Investigators. *Diabetes Care*. 1998; 21(10):1589–1595. [PubMed: 9773716]

25. Bonds D, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia*. 2006; 49(3):459–468. [PubMed: 16440209]
26. Friday K, Dong C, Fontenot R. Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab*. 2001; 86(1):48–52. [PubMed: 11231977]
27. Andersson B, Mattsson L, Hahn L, et al. Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1997; 82(2):638–643. [PubMed: 9024268]
28. Samaras K, Hayward C, Sullivan D, Kelly R, Campbell L. Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study. *Diabetes Care*. 1999; 22(9):1401–1407. [PubMed: 10480500]

Appendix

Pennington Biomedical Research Center (Baton Rouge, LA)

George A. Bray, MD*

Iris W. Culbert, BSN, RN, CCRC**

Catherine M. Champagne, PhD, RD

Barbara Eberhardt, RD, LDN

Frank Greenway, MD

Fonda G. Guillory, LPN

April A. Herbert, RD

Michael L. Jeffirs, LPN

Betty M. Kennedy, MPA

Jennifer C. Lovejoy, PhD

Laura H. Morris, BS

Lee E. Melancon, BA, BS

Donna Ryan, MD

Deborah A. Sanford, LPN

Kenneth G. Smith, BS, MT

Lisa L. Smith, BS

Julia A. St.Amant, RTR

* denotes Principal Investigator

** denotes Program Coordinator

Richard T. Tulley, PhD

Paula C. Vicknair, MS, RD

Donald Williamson, PhD

Jeffery J. Zachwieja, PhD

University of Chicago (*Chicago, IL*)

Kenneth S. Polonsky, MD^{*}

Janet Tobian, MD, PhD^{*}

David Ehrmann, MD^{*}

Margaret J. Matulik, RN, BSN^{**}

Bart Clark, MD

Kirsten Czech, MS

Catherine DeSandre, BA

Ruthanne Hilbrich, RD

Wylie McNabb, EdD

Ann R. Semenske, MS, RD

Jefferson Medical College (*Philadelphia, PA*)

Jose F. Caro, MD^{*}

Pamela G. Watson, RN, ScD^{*}

Barry J. Goldstein, MD, PhD^{*}

Kellie A. Smith, RN, MSN^{**}

Jewel Mendoza, RN, BSN^{**}

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Constance Pepe, MS, RD

John Spandorfer, MD

University of Miami (*Miami, FL*)

Richard P. Donahue, PhD^{*}

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Ronald Prineas, MD, PhD^{*}

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Lascelles Kirby, MS
Carmen Larreal
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Jadell Mendez
Juliet Ojito, RN
Arlette Perry, PhD
Patrice Saab, PhD

The University of Texas Health Science Center (San Antonio, TX)

Steven M. Haffner, MD, MPH^{*}
Maria G. Montez, RN, MSHP, CDE^{**}
Carlos Lorenzo, MD, PhD
Arlene Martinez, RN, BSN, CDE

University of Colorado (Denver, CO)

Richard F. Hamman, MD, DrPH^{*}
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B. Ned Calonge, MD, MPH
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Sheila C. Steinke, MS
Brent VanDorsten, PhD

Joslin Diabetes Center (Boston, MA)

Edward S. Horton, MD*
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Stacy Rubtchinsky, BS
Ellen W. Seely, MD

Dana Schweizer, BSN

Donald Simonson, MD

Fannie Smith, MD

Caren G. Solomon, MD, MPH

James Warram, MD

***VA Puget Sound Health Care System and University of Washington
(Seattle, WA)***

Steven E. Kahn, MB, ChB^{*}

Brenda K. Montgomery, RN, BSN, CDE^{**}

Wilfred Fujimoto, MD

Robert H. Knopp, MD

Edward W. Lipkin, MD

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Dace Trence, MD

University of Tennessee (Memphis, TN)

Abbas E. Kitabchi, PhD, MD, FACP^{*}

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Northwestern University's Feinberg School of Medicine (Chicago, IL)

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Massachusetts General Hospital (Boston, MA)

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Enrico Cagliero, MD

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Valerie Goldman, MS, RD

Alexandra Poulos

University of California-San Diego (San Diego, CA)

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Sundar Mudaliar, MD

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Jean Smith, RN

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St. Luke's-Roosevelt Hospital (New York, NY)

F. Xavier Pi-Sunyer, MD*

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Carmen Pal, MD

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Kristine A. Viscovich, ANP

Indiana University (Indianapolis, IN)

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Melvin J. Prince, MD*

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Paris J. Roach, MD

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Medstar Research Institute (Washington, DC)

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Peggy Gibbs

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Maureen Passaro, MD

Gabriel Uwaifo, MD

University of Southern California/UCLA Research Center (Alhambra, CA)

Mohammed F. Saad, MD*

Maria Budget**

Sujata Jinagouda, MD**

Khan Akbar, MD

Claudia Conzues

Perpetua Magpuri

Kathy Ngo

Amer Rassam, MD

Debra Waters

Kathy Xaphthalmous

Washington University (St. Louis, MO)

Julio V. Santiago, MD* (deceased)

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Ana Santiago, RD**

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Lucy Ryder, RN

Cormarie Wernimont, MS, RD

Johns Hopkins School of Medicine (Baltimore, MD)

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Jeanne B. Charleston, RN, MSN

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Dawn Jiggetts

Deloris Johnson

Hope Joseph

Kimberly Loman

Henry Mosley

Richard R. Rubin, PhD

Alafia Samuels, MD

Kerry J. Stewart, EdD

Paula Williamson

University of New Mexico (Albuquerque, NM)

David S. Schade, MD*

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Mark R. Burge, MD

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Ysela Gonzales, RN, MSN

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Patricia Katz, LPN

Carolyn King

Amer Rassam, MD

Sofya Rubinchik, MD

Willette Senter, RD

Debra Waters, PhD

Albert Einstein College of Medicine (Bronx, NY)

Harry Shamoon, MD*

Janet O. Brown, RN, MPH, MSN**

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Jill Crandall, MD

Helena Duffy, MS, C-ANP

Samuel Engel, MD

Allison Friedler, BS

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Nadege Longchamp, LPN

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Dorothy Pompei, BA

Jonathan Scheindlin, MD

Elissa Violino, RD, MS

Elizabeth Walker, RN, DNSc, CDE

Judith Wylie-Rosett, EdD, RD

Elise Zimmerman, RD, MS

Joel Zonszein, MD

University of Pittsburgh (Pittsburgh, PA)

Trevor Orchard, MD*

Rena R. Wing, PhD*

Gaye Koenning, MS, RD**

M. Kaye Kramer, BSN, MPH**

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Miriam Boraz
Lisa Clifford, BS
Rebecca Culyba, BS
Marlene Frazier
Ryan Gilligan, BS
Susan Harrier, MLT
Louann Harris, RN
Susan Jeffries, RN, MSN
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Cheryl F. Smith, PhD
Marie Smith, RN, BSN
Elizabeth Venditti, PhD
Valarie Weinzierl, BS
Katherine V. Williams, MD, MPH
Tara Wilson, BA

University of Hawaii (Honolulu, HI)

Richard F. Arakaki, MD^{*}
Renee W. Latimer, BSN, MPH^{**}
Narleen K. Baker-Ladao, BS
Ralph Beddow, MD
Lorna Dias, AA
Jillian Inouye, RN, PhD
Marjorie K. Mau, MD

Kathy Mikami, BS, RD

Pharis Mohideen, MD

Sharon K. Odom, RD, MPH

Raynette U. Perry, AA

Southwest American Indian Centers (Phoenix, AZ; Shiprock, NM; Zuni, NM)

William C. Knowler, MD, DrPH^{*,+}

Norman Coeate^{**}

Mary A. Hoskin, RD, MS^{**}

Carol A. Percy, RN, MS^{**}

Kelly J. Acton, MD, MPH

Vickie L. Andre, RN, FNP

Rosalyn Barber

Shandiin Begay, MPH

Peter H. Bennett, MB, FRCP

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Evelyn C. Bird, RD, MPH

Brenda A. Broussard, RD, MPH, MBA,

CDE

Marcella Chavez, RN, AS

Tara Dacawyma

Matthew S. Doughty, MD

Roberta Duncan, RD

Cyndy Edgerton, RD

Jacqueline M. Ghahate

Justin Glass, MD

Martia Glass, MD

Dorothy Gohdes, MD

⁺denotes Genetics Group members

Wendy Grant, MD
Robert L. Hanson, MD, MPH
Ellie Horse
Louise E. Ingraham, MS, RD, LN
Merry Jackson
Priscilla Jay
Roylen S. Kaskalla
David Kessler, MD
Kathleen M. Kobus, RNC-ANP
Jonathan Krakoff, MD
Catherine Manus, LPN
Sara Michaels, MD
Tina Morgan
Yolanda Nashboo (deceased)
Julie A. Nelson, RD
Steven Poirier, MD
Evette Polczynski, MD
Mike Reidy, MD
Jeanine Roumain, MD, MPH
Debra Rowse, MD
Sandra Sangster
Janet Sewenemewa
Darryl Tonemah, PhD
Charlton Wilson, MD
Michelle Yazzie

George Washington University Biostatistics Center (DPP Coordinating Center Rockville, MD)

Raymond Bain, PhD*
Sarah Fowler, PhD*

Tina Brenneman**

Solome Abebe

Julie Bamdad, MS

Jackie Callaghan

Sharon L. Edelstein, ScM

Yuping Gao

Kristina L. Grimes

Nisha Grover

Lori Haffner, MS

Steve Jones

Tara L. Jones

Richard Katz, MD

John M. Lachin, ScD

Pamela Mucik

Robert Orlosky

James Rochon, PhD

Alla Sapozhnikova

Hanna Sherif, MS

Charlotte Stimpson

Marinella Temprosa, MS

Fredricka Walker-Murray

Central Biochemistry Laboratory (Seattle, WA)

Santica Marcovina, PhD, ScD*

Greg Strylewicz, PhD**

F. Alan Aldrich

Epidemiological Cardiology Research Center- Epicare (Winston-Salem, NC)

Pentti Rautaharju, MD, PhD*

Ronald J. Prineas, MD, PhD*/*

Teresa Alexander

Charles Campbell, MS

Sharon Hall

Yabing Li, MD

Margaret Mills

Nancy Pemberton, MS

Farida Rautaharju, PhD

Zhuming Zhang, MD

NIH/NIDDK (Bethesda, MD)

R. Eastman, MD

Judith Fradkin, MD

Sanford Garfield, PhD

Nutrition Coding Center (Columbia, SC)

Elizabeth Mayer-Davis, PhD*

Robert R. Moran, PhD**

Quality of Well-Being Center (La Jolla, CA)

Ted Ganiats, MD*

Kristin David, MHP*

Andrew J. Sarkin, PhD*

+ Genetics Working Group

Jose C. Florez, MD, PhD^{1, 2}

David Altshuler, MD, PhD^{1, 2}

Paul I.W. de Bakker, PhD²

Paul Franks, PhD, Mphil, MS^{3, 6}

Robert L. Hanson, MD, MPH³

Kathleen Jablonski, PhD⁵

William C. Knowler, MD, DrPH³

¹Massachusetts General Hospital

²Broad Institute

³NIDDK

⁶Umeå University, Sweden

⁵Coordinating Center

Jarred McAteer, AB^{1, 2}

Toni I. Pollin, PhD⁴

Alan R. Shuldiner, MD⁴

\$watermark-text

\$watermark-text

\$watermark-text

⁴University of Maryland

Table 1
Baseline Characteristics of Premenopausal and Postmenopausal Women in the Diabetes Prevention Program, 1996–1999.

	Premenopausal N=708	Postmenopausal N=529	P-value ^a	Natural menopause N=528	P-value ^b	Bilateral oophorectomy N=201	P-value ^c
Age (years, mean, SD)	45.7 (3.6)	55.1 (5.4)	<.0001	56.4 (4.6)	<.0001	53.0 (6.0)	<.0001
Race/ethnicity (n, %)			0.44		0.77		0.38
Non-Hispanic white	380 (54)	290 (55)		173 (53)		117 (58)	
African-American	141 (20)	114 (22)		72 (22)		42 (21)	
Hispanic	113 (16)	84 (16)		55 (17)		29 (14)	
Native American/American Indian	50 (7)	24 (5)		17 (5)		7 (3)	
Asian/Pacific Islander	24 (3)	17 (3)		11 (3)		6 (3)	
Family history of diabetes (n, %)	516 (73)	358 (68)	0.047	218 (66)	0.03	140 (70)	0.37
Smoking (n, %)	39 (6)	39 (7)	0.18	21 (6)	0.57	18 (9)	0.08
History of gestational diabetes (n, %)	159 (22)	26 (5)	<.0001	18 (5.5)	<.0001	9 (4)	<.0001
At least one pregnancy (n, %)	604 (85)	457 (86)	0.59	292 (89)	0.10	165 (82)	0.26
Time since menopause (years, mean, SD)	not applicable	10.0 (8.3)		8.4 (7.6)		12.5 (11.3)	
Time since menopause, (years, median, interquartile range)	not applicable	7.7 (4.2–14.5)		6.7 (3.5–10.7)		11.0 (6.0–17.1)	
Hysterectomy (n, %)	2 (0.3)	220 (42)	<.0001	20 (6.1)	<.0001	200 (100)	<.0001
Unilateral or partial oophorectomy (n, %)	21 (3)	20 (4)	0.16	20 (6)	0.016	0	--
Currently using hormone therapy (n, %)	0	268 (51)	<.00001	129 (39)	<.00001	139 (69)	<.00001
Ever used hormone therapy (n, %)	23 (3)	350 (66)	<.00001	174 (53)	<.00001	176 (88)	<.00001
Ever used oral contraception (n, %)	543 (77)	340 (64)	<.00001	209 (64)	<.00001	70 (35)	0.001
Currently using oral contraception (n, %)	44 (6)	0	<.00001	0	<.00001	0	<.00001
Weight (kg, mean, SD)	93.7 (20.2)	89.3 (19.1)	<.0001	87.5 (18.8)	<.0001	92.2 (19.2)	0.34
Body mass index (kg/m ² , mean, SD)	35.3 (6.8)	34.1 (6.8)	0.002	33.5 (6.5)	<.0001	35.1 (7.2)	0.74
Waist circumference (cm, mean, SD)	104.0 (15.0)	102.4 (13.9)	0.058	101.3 (13.8)	.006	104.3 (14.0)	0.84
Fasting plasma glucose (mg/dl, mean, SD)	105.7 (8.2)	106.1 (8.3)	0.44	105.7 (7.9)	.99	106.6 (8.8)	0.16
2-hour glucose (mg/dl, mean, SD)	164.1 (17.2)	163.8 (17.0)	0.69	163.5 (17.2)	.57	164.2 (16.6)	0.97
Fasting insulin (uU/ml, mean, SD)	26.9 (13.9)	25.1 (13.9)	0.023	24.2 (14.1)	.003	26.6 (13.5)	0.76
Corrected insulin response (mean, SD)	0.7 (0.4)	0.6 (0.4)	0.24	0.6 (0.4)	.025	0.7 (0.5)	0.48
C-reactive protein (mg/dl, mean, SD)	0.7 (0.4)	0.6 (0.4)	0.27	.6 (7)	.40	0.8 (0.7)	0.001
Fibrinogen (mg/dl, mean, SD)	390.0 (84.3)	403.4 (80.8)	0.005	401.5 (82.0)	.040	406.5 (78.9)	0.014

	Premenopausal N=708	Postmenopausal N=529	P-value ^a	Natural menopause N=328	P-value ^b	Bilateral oophorectomy N=201	P-value ^c
Adiponectin (mg/ml, mean, SD)	7.5 (2.8)	9.6 (3.9)	<0.0001	9.89 (4.15)	<.001	9.1 (3.4)	<0.0001
Tissue plasminogen activator antigen (ng/ml, mean, SD)	11.1 (4.1)	10.6 (3.7)	0.013	10.9 (3.7)	.37	10.1 (3.6)	<0.001
Randomization arm (n, %)			0.08		0.07		0.54
Randomized to intensive lifestyle (n, %)	220 (31)	177 (33)		111 (34)		66 (33)	
Randomized to metformin (n, %)	229 (32)	191 (36)		121 (37)		70 (35)	
Randomized to placebo (n, %)	259 (37)	161 (30)		96 (29)		65 (32)	

^a p-value for premenopause vs. postmenopause

^b p-value for premenopause vs. natural menopause

^c p-value for premenopause vs. bilateral oophorectomy

Table 2

Hazard Ratio (HR, 95% confidence interval) of Progression to Diabetes by Menopause Status. Reference Is Premenopausal Women; an HR > 1 Indicates Greater Diabetes Risk Among Postmenopausal Women.

Among all women in sample	Lifestyle	Metformin	Placebo
Unadjusted	0.46	0.26, 0.83	1.35 0.88, 2.06 0.98 0.68, 1.41
Adjusted for age	0.63	0.28, 1.44	1.24 0.67, 2.29 1.05 0.63, 1.74
Adjusted for above, and age, race/ethnicity, family history of diabetes, history of GDM	0.68	0.29, 1.56	1.25 0.66, 2.33 1.21 0.71, 2.04
Adjusted for above, and waist circumference	0.62	0.26, 1.48	1.24 0.66, 2.33 1.23 0.73, 2.09
Adjusted for above, and 1/fasting insulin, CIR	0.65	0.27, 1.54	1.26 0.66, 2.40 1.21 0.71, 2.07
Among premenopausal women vs. postmenopausal women in natural menopause			
Unadjusted	0.65	0.36, 1.20	1.21 0.74, 1.98 0.90 0.57, 1.41
Adjusted for age	1.28	0.51, 3.21	1.05 0.46, 2.42 0.88 0.44, 1.75
Adjusted for above, and age, race/ethnicity family history of diabetes, history of GDM	1.54	0.61, 3.91	1.04 0.45, 2.41 0.99 0.49, 1.98
Adjusted for above, and waist circumference	1.48	0.55, 3.96	1.02 0.44, 2.38 1.01 0.50, 2.03
Adjusted for above, and 1/fasting insulin, CIR	1.43	0.54, 3.78	1.02 0.43, 2.42 0.89 0.44, 1.79
Among premenopausal women vs. postmenopausal women with bilateral oophorectomy			
Unadjusted	0.16	0.04, 0.64	1.58 0.92, 2.70 1.11 0.68, 1.79
Adjusted for age	0.22	0.05, 1.02	1.26 0.63, 2.52 1.06 0.59, 1.90
Adjusted for above, and age, race/ethnicity family history of diabetes, history of GDM	0.22	0.05, 1.04	1.28 0.64, 2.55 1.24 0.68, 2.27
Adjusted for above, and waist circumference	0.18	0.04, 0.91	1.27 0.63, 2.54 1.26 0.69, 2.31
Adjusted for above, and 1/fasting insulin, CIR	0.19	0.04, 0.94	1.29 0.63, 2.64 1.37 0.74, 2.55

Table 3

Hazard Ratio (HR, 95% confidence interval) of Progression to Diabetes by Menopause Status, Stratified by Hormone Therapy Use. Reference is Premenopausal women; an HR > 1 Indicates Greater Diabetes Risk Among Postmenopausal Women.

Among premenopausal women and all postmenopausal women not using HT					
		Lifestyle	Metformin	Placebo	
Unadjusted	0.51	0.25, 1.01	1.53 0.91, 2.58	1.11 0.71, 1.72	
Adjusted for age	0.93	0.34, 2.50	1.39 0.60, 3.18	1.05 0.56, 1.99	
Adjusted for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, 1/fasting insulin, CIR	0.80	0.28, 2.28	1.22 0.52, 2.87	1.10 0.57, 2.14	
Among premenopausal women (n=708) and naturally postmenopausal women using HT (n=129)					
Unadjusted	0.86	0.36, 2.02	0.97 0.48, 1.94	0.54 0.22, 1.32	
Adjusted for age	1.55	0.47, 5.17	0.68 0.24, 1.93	0.45 0.15, 1.32	
Adjusted for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, 1/fasting insulin, CIR	1.57	0.46, 5.28	0.81 0.28, 2.39	0.60 0.20, 1.84	
Among premenopausal women (n=708) and naturally postmenopausal women not using HT (n=199)					
Unadjusted	0.55	0.26, 1.18	1.44 0.80, 2.56	1.07 0.66, 1.75	
Adjusted for age	1.22	0.42, 3.57	1.26 0.49, 3.27	1.02 0.49, 2.13	
Adjusted for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, 1/fasting insulin, CIR	1.32	0.41, 4.31	1.05 0.40, 2.77	0.94 0.45, 1.97	
Among premenopausal women (n=708) and surgically postmenopausal women using HT (n=139)					
Unadjusted		0 surgically postmenopausal women using HT developed diabetes in the lifestyle arm	1.49 0.81, 2.74	1.07 0.61, 1.85	
Adjusted for age			1.03 0.56, 2.58	1.04 0.53, 2.01	
Adjusted for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, 1/fasting insulin, CIR			1.23 0.56, 2.68	1.29 0.65, 2.57	
Among premenopausal women (n=708) and surgically postmenopausal women not using HT (n=62)					
Unadjusted	0.38	0.09, 1.58	1.82 0.77, 4.29	1.23 0.57, 2.83	
Adjusted for age	0.61	0.12, 3.09	1.35 0.48, 3.81	1.06 0.43, 2.61	
Adjusted for age, race/ethnicity, family history of diabetes, history of GDM, waist circumference, 1/fasting insulin, CIR	0.41	0.08, 2.16	1.22 0.39, 3.83	1.53 0.58, 4.01	