Lipoprotein Particle Size and Concentration by Nuclear Magnetic Resonance and Incident Type 2 Diabetes in Women

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OBJECTIVE—Diabetic dyslipoproteinemia is characterized by low HDL cholesterol and high triglycerides. We examined the association of lipoprotein particle size and concentration measured by nuclear magnetic resonance (NMR) spectroscopy with clinical type 2 diabetes.

RESEARCH DESIGN AND METHODS—This was a prospective study of 26,836 initially healthy women followed for 13 years for incident type 2 diabetes (n = 1,657). Baseline lipids were measured directly and lipoprotein size and concentration by NMR. Cox regression models included nonlipid risk factors (age, race, smoking, exercise, education, menopause, blood pressure, BMI, family history, AIC, and C-reactive protein). NMR lipoproteins were also examined after further adjusting for standard lipids.

RESULTS—Incident diabetes was significantly associated with baseline HDL cholesterol, triglycerides, and NMR-measured size and concentration of LDL, IDL, HDL, and VLDL particles. The associations of these particles differed substantially by size. Small LDLNMR and small HLDLNMR were positively associated with diabetes (quintile 5 vs. 1 [adjusted hazard ratios and 95% CIs], 4.04 [3.21–5.09] and 1.84 [1.54–2.19], respectively). By contrast, large LDLNMR and large HLDLNMR were inversely associated (quintile 1 vs. 5, 2.50 [2.12–2.95] and 4.51 [3.68–5.52], respectively). For VLDLNMR, large particles imparted higher risk than small particles (quintile 5 vs. 1, 3.11 [2.35–4.11] and 1.31 [1.10–1.55], respectively). Lipoprotein particle size remained significant after adjusting for standard lipids and nonlipid factors.

CONCLUSIONS—In this prospective study of women, NMR lipoprotein size and concentrations were associated with incident type 2 diabetes and remained significant after adjustment for established risk factors, including HDL cholesterol and triglycerides. Diabetes 59:1153–1160, 2010

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and 3) whether they provide additive risk information to established risk factors for diabetes.

RESEARCH DESIGN AND METHODS

Study participants were drawn from the Women's Health Study (WHS), a completed randomized, double-blinded, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease (CVD) and cancer in women (11–13). WHS participants were apparently healthy female health care professionals, aged ≥45 years, who were free of self-reported CVD and cancer at study entry (1992–1995). At the time of enrollment, women gave written informed consent and completed questionnaire on demographics, anthropometrics, medical history, and lifestyle factors. They were also asked to provide a baseline blood sample; 28,345 women did so, and of these, 98.5% (n = 27,909) had NMR measurements. For this study, we excluded women missing other lipids (n = 33), those with self-reported baseline type 2 diabetes (n = 770), and those with baseline A1C ≥6.5% (n = 270), leaving 26,836 women for analysis. We also repeated the analyses after excluding 169 women with A1C ≥6.0 and <6.5% with similar results. P value for linear trend was obtained using the quantile number as a predictor. All P values were two-tailed.

RESULTS

During a median follow-up of 13.3 years (interquartile range 12.3–13.8), a total of 1,687 incident cases of clinical type 2 diabetes occurred. Table 1 shows the baseline characteristics of participants according to the development of diabetes during follow-up. In comparison with the small differences noted in LDL cholesterol between case subjects and noncase subjects, the NMR-measured concentration of total LDLNMR particles was much higher in case subjects. This resulted from case subjects having more small LDLNMR and IDLNMR particles but fewer large LDLNMR particles. Case subjects also had significantly less HDLNMR particles (total) due to having fewer large HDLNMR particles, despite having more small HDLNMR particles, VLDLNMR particles were higher in case subjects (both large and small). In accordance with these results, average particle size in case versus control subjects was smaller for LDLNMR and HDLNMR, and larger for VLDLNMR.

LDL measures. HRs for diabetes according to quintiles of LDL cholesterol and LDLNMR particle concentration and size are shown in Table 2. In fully adjusted models, neither total cholesterol (data not shown) nor LDL cholesterol was associated with diabetes (P for trend 0.53 and 0.64, respectively), but other LDL measures, such as LDLNMR particle concentration and size, were significantly associated with diabetes (P for trend <0.001).

LDLNMR particles differed substantially in their association with diabetes according to their size. Large LDLNMR particles were inversely associated (adjusted HR 2.50 [95% CI 2.12–2.95]) for quintile 1 vs. 5, while small LDLNMR particles were positively associated with diabetes (4.04 [3.21–5.09]) for quintile 5 vs. 1. The concentration of certain lipids may be superior to fasting concentrations for risk prediction (21,22), we examined whether fasting status modified the association of NMR lipoproteins with diabetes. Statistical tests for interaction between fasting status and lipoproteins in relation to diabetes were obtained using likelihood ratio tests.

We repeated the analyses after excluding 169 women with A1C ≥6.0 and <6.5% with similar results. P value for linear trend was obtained using the quantile number as a predictor. All P values were two-tailed.
the higher the risk. Associations obtained from the minimally adjusted model 1 were generally stronger than model 2, which had further adjustment for other factors.

**HDL measures.** HDL cholesterol was inversely associated with diabetes (Table 3), with quintile 1 vs. 5 associated with fourfold increased risk. While total HDLNMR particle concentration was also inversely associated with diabetes (quintile 1 vs. 5, adjusted HR 1.20 [95% CI 1.03–1.40]), it was only large HDLNMR particles that were inversely associated, with quintile 1 vs. 5 (adjusted HR 1.20 [95% CI 1.03–1.40]). Interestingly, this inverse association noted for large HDLNMR particles was not noted for smaller HDLNMR particles. Instead, there was nearly twofold increased risk associated with the highest concentration of small HDLNMR particles. This was also reflected in HDLNMR average particle size, with smaller HDLNMR size having 4.5-fold higher risk of diabetes.

**VLDL measures.** Higher concentrations of triglycerides and triglyceride-rich VLDL particles were associated with higher risk of diabetes (Table 4). Large VLDLNMR Particles, which carry more triglycerides than smaller particles and correlate more with insulin resistance (9), had the strongest association of the VLDL particles with diabetes, with more than threefold increased risk for quintile 5 vs. 1. Small VLDLNMR also showed positive association with diabetes but less than large particles. Thus, larger average VLDLNMR size correlated with higher risk of diabetes, although not to the same extent as smaller LDLNMR or HDLNMR size, both of which had higher absolute and relative risk.

Figure 1 summarizes the adjusted HRs and 95% CIs for incident diabetes associated with extreme quintiles of the NMR lipoproteins, standard lipids, and A1C, ranked according to the magnitude of the HRs.

**Other analyses.** When we repeated the analyses using continuous variables instead of quintiles, similar results were obtained. Similar results were also found after additionally excluding 169 women with A1C ≥6.0%. A similar pattern of findings was noted when analyses were stratified by median follow-up time into the first and second 6 years. Overall, stronger associations were noted for A1C and NMR lipoproteins with diabetes during the first 6 years compared with the second 6 years of follow-up, but the relative magnitude of associations was generally similar and significant both early and late in follow-up. For example, the adjusted HRs (95% CIs) for extreme quintile values of LDLNMR, HDLNMR, and VLDLNMR size were 6.56

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### TABLE 1

Baseline characteristics of participants according to incident type 2 diabetes

|                     | No diabetes | Diabetes | P*  |
|---------------------|-------------|----------|-----|
| n                   | 25,149      | 1,687    | 0.96|
| Age (years)         | 54.6 ± 7.10 | 54.6 ± 6.55 | 0.04|
| Current smoking (%) | 11.5        | 13.2     | 0.04|
| Hypertension (%)    | 22.4        | 47.0     | <0.001|
| Postmenopausal status (%) | 54.0 | 55.6 | <0.001|
| Postmenopausal hormone use (%) | 44.3 | 40.4 | 0.002|
| Fasting (%)         | 75.8        | 78.6     | 0.01|
| BMI (kg/m²)         | 25.4 ± 4.6  | 30.6 ± 5.9 | <0.001|
| A1C (%)             | 4.98 (4.83–5.15) | 5.28 (5.07–5.53) | <0.001|
| Family history of diabetes (%) | 23.4 | 43.9 | <0.001|
| hsCRP (mg/l)        | 1.84 (0.74–3.98) | 4.42 (2.26–7.34) | <0.001|
| Lipid concentrations (mg/dl) |             |          |     |
| Total cholesterol   | 208 (184–235) | 213 (187–242) | <0.001|
| LDL cholesterol     | 121 (100–144) | 126 (104–152) | <0.001|
| HDL cholesterol     | 53 (44–63)   | 42 (36–50)  | <0.001|
| Triglycerides       | 115 (82–167) | 175 (126–247) | <0.001|
| NMR lipoprotein particle concentrations |             |          |     |
| LDLNMR (nmol/l)     |             |          |     |
| Total               | 1,260 (1,024–1,570) | 1,587 (1,288–1,944) | <0.001|
| Large               | 551 (414–692) | 424 (268–589) | <0.001|
| Small               | 632 (382–972) | 1,075 (714–1,502) | <0.001|
| IDLNMR              | 32 (10–66)   | 51 (22–93)  | <0.001|
| HDLNMR (μmol/l)     |             |          |     |
| Total               | 35.1 (31.2–39.5) | 34.2 (30.1–39.0) | <0.001|
| Large               | 7.8 (5.3–10.5) | 4.6 (3.0–6.8)  | <0.001|
| Medium              | 2.7 (0.8–6.0)  | 2.7 (0.8–5.8)  | 0.08|
| Small               | 23.6 (19.9–27.2) | 25.5 (22.0–28.8) | <0.001|
| VLDLNMR (nmol/l)    |             |          |     |
| Total               | 68.0 (48.9–90.1) | 73.8 (55.1–94.6) | <0.001|
| Large               | 1.3 (0.3–3.6)  | 3.0 (1.4–5.5)  | <0.001|
| Medium              | 20.8 (11.1–31.8) | 20.9 (11.9–32.6) | 0.13|
| Small               | 44.5 (32.2–57.8) | 48.2 (36.7–59.9) | <0.001|
| NMR average particle size (nm) |             |          |     |
| LDLNMR size         | 21.4 (20.9–21.9) | 20.7 (20.1–21.3) | <0.001|
| HDLNMR size         | 9.0 (8.7–9.4)  | 8.6 (8.4–8.9)  | <0.001|
| VLDLNMR size        | 46.3 (42.0–51.6) | 51.1 (46.6–56.7) | <0.001|

Data are median (interquartile range) or means ± SD, unless otherwise indicated. *P values were obtained from Student t test for continuous variables expressed as means, from Wilcoxon rank-sum tests for variables expressed as medians, and χ² tests for categorical variables. 

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Data are HR (95% CI) and (ranges minimum–maximum) and are given for each quintile. See Table 2 legend for model adjustments.

When we evaluated all nine NMR-measured lipoprotein particle concentrations in one model that also adjusted for nonlipid risk factors, we found that large and small LDL NMR, large and small HDL NMR, and large VLDL NMR particles were no longer significant ($P = 0.38$ and $0.62$, respectively). Medium HDL NMR and medium VLDL NMR particles now showed inverse associations with diabetes.

### TABLE 2
Association of LDL measures with incident type 2 diabetes

| LDL measure (mg/dl) | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | $P$ for trend |
|---------------------|------------|------------|------------|------------|------------|---------------|
| LDL cholesterol | 0.99 (0.85–1.16) | 1.14 (0.98–1.33) | 1.10 (0.94–1.29) | 1.57 (1.35–1.82) | >0.001 |
| Model 1 | Referent | Referent | Referent | Referent | Referent | Referent |
| Model 2 | Referent | Referent | Referent | Referent | Referent | Referent |

### TABLE 3
Association of HDL measures with incident type 2 diabetes

| HDL measure (mg/dl) | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | $P$ for trend |
|---------------------|------------|------------|------------|------------|------------|---------------|
| HDL cholesterol | 39.9–46.3 | 46.4–52.8 | 52.9–61.8 | >61.8 | | |
Women were more likely to be hypertensive and hormone-related ratios significantly associated (LDLNMR, HDLNMR, or VLDLNMR particle size to models that already included standard lipids and nonlipid risk factors. Although the associations were attenuated, larger VLDLNMR particle size (quintile 5 vs. 1, 2.04 [1.63–2.56]; P for trend <0.001). The change in the likelihood ratio $\chi^2$ tests was significant for adding either LDLNMR, HDLNMR, or VLDLNMR particle size to models that already included standard lipids and nonlipid risk factors (change in $\chi^2$ 24.53, 48.56, and 59.51, respectively; $P < 0.0001$ for all three).

Finally, we identified 8,101 women (number of incident diabetes cases = 132) who had normal values of both triglycerides and HDL cholesterol using median values as cut points (triglycerides <117 mg/dl and HDL cholesterol >52 mg/dl). Compared with the rest of the cohort, these women were more likely to be hypertensive and hormone users. We then examined the association of small LDLNMR with incident diabetes in these women after adjusting for nonlipid risk factors (including hypertension and hormone use). Higher concentration of small LDLNMR particles was significantly associated (P for trend 0.005) with incident diabetes, despite that these women had normal levels of triglycerides and HDL cholesterol (fully adjusted HR for the top versus bottom quintile of small LDLNMR 3.95 [95% CI 1.69–9.55]).

**DISCUSSION**

Consistent with prior studies in individuals with insulin resistance, we found that in initially healthy women followed prospectively for incident clinical type 2 diabetes, both triglycerides and HDL cholesterol were independently associated with diabetes but not LDL or total cholesterol. Furthermore, NMR-measured size and concentrations of LDL, HDL, and VLDL particles were also associated with diabetes, independent of triglycerides, HDL cholesterol, and other factors. The associations of lipoprotein particles differed markedly by size. Smaller average size of LDLNMR and HDLNMR particles, as well as the concentration of small LDLNMR and HDLNMR particles, was associated with increased risk, while the concentration of large LDLNMR and HDLNMR particles carried lower risk. Large VLDLNMR particles carried higher risk than small particles. LDLNMR, HDLNMR, and VLDLNMR particle size remained associated with diabetes in models that already included standard lipids and nonlipid risk factors, adding incremental risk information beyond that obtained from established risk factors.

A uniting feature of these lipoprotein alterations and their association with type 2 diabetes may be a state of insulin resistance. The associations we found in this study in relation to the NMR-measured lipoproteins have been previously linked to insulin resistance as measured by the euglycemic clamp (9). Garvey et al. (9) demonstrated a progressive increase in insulin resistance associated with larger VLDLNMR size, smaller LDLNMR size, and smaller HDLNMR size, all of which are consistent with our findings in relation to predicting incident type 2 diabetes. In 830 subjects with insulin resistance followed in the Insulin Resistance Atherosclerosis Study over a 5-year period, NMR-measured larger VLDLNMR size and smaller HDLNMR particles were independently associated with increased risk of type 2 diabetes (14), while LDLNMR size and LDLNMR particles were not significant independent of other risk factors. Factor analysis revealed a single factor that correlated with insulin resistance accounted for nearly half the variance in these lipoprotein measures (10).

Our study, which was conducted in a large population of healthy women, found independent associations for incident diabetes with baseline LDLNMR size and concentrations, with larger LDLNMR particles associated with lower risk and smaller LDLNMR particles associated with higher risk. Moreover, small LDLNMR imparted higher risk of diabetes even in women with normal triglyceride and HDL cholesterol levels. The inverse association of large LDLNMR particles with type 2 diabetes contrasts with the

### TABLE 4

Association of VLDL measures with incident type 2 diabetes

| Triglycerides (mg/dl) | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P for trend |
|-----------------------|------------|------------|------------|------------|------------|-------------|
| Model 1               | ≤70        | 71–95      | 96–125     | 126–178    | >178       | <0.0001     |
| Model 2               | Referent   | 1.73 (1.30–2.31) | 2.47 (1.88–3.25) | 4.91 (3.81–6.33) | 8.88 (6.94–11.37) | <0.0001     |
| Model 2               | Referent   | 1.36 (1.10–1.83) | 1.57 (1.18–2.08) | 2.57 (1.98–3.35) | 3.71 (2.87–4.80) | <0.0001     |
| LDLNMR particle concentrations | Total LDLNMR (nmol/l) | ≤45.6 | 45.7–61.8 | 61.9–77.2 | 77.3–96.8 | >96.8 |
|                       | Model 1    | Referent   | 1.41 (1.19–1.67) | 1.62 (1.38–1.91) | 1.70 (1.44–2.00) | 1.81 (1.54–2.13) | <0.0001     |
|                       | Model 2    | Referent   | 1.18 (0.99–1.41) | 1.16 (0.98–1.38) | 1.25 (1.05–1.48) | 1.26 (1.06–1.50) | 0.01         |
|                       | Large LDLNMR (nmol/l) | ≤0.1 | 0.2–0.5 | 0.6–1.8 | 1.9–3.8 | >3.8 |
|                       | Model 1    | Referent   | 1.58 (1.16–2.14) | 3.57 (2.71–4.70) | 5.41 (4.12–7.09) | 6.66 (5.10–8.70) | <0.0001     |
|                       | Model 2    | Referent   | 1.49 (1.09–2.05) | 2.54 (1.91–3.39) | 2.98 (2.24–3.96) | 3.11 (2.35–4.11) | <0.0001     |
|                       | Medium LDLNMR (nmol/l) | ≤8.2 | 8.3–15.9 | 16.0–23.8 | 23.9–34.1 | >34.1 |
|                       | Model 1    | Referent   | 1.11 (0.95–1.30) | 1.08 (0.92–1.27) | 1.07 (0.91–1.26) | 1.15 (0.98–1.35) | 0.19         |
|                       | Model 2    | Referent   | 1.03 (0.88–1.22) | 0.99 (0.84–1.18) | 0.89 (0.75–1.05) | 1.04 (0.88–1.35) | 0.73         |
|                       | Small LDLNMR (nmol/l) | ≤31.5 | 31.6–42.1 | 42.2–51.5 | 51.6–63.1 | >63.1 |
|                       | Model 1    | Referent   | 1.50 (1.28–1.76) | 1.69 (1.44–1.98) | 1.79 (1.53–2.11) | 1.87 (1.59–2.20) | <0.0001     |
|                       | Model 2    | Referent   | 1.13 (0.96–1.34) | 1.11 (0.94–1.31) | 1.22 (1.03–1.44) | 1.31 (1.10–1.55) | 0.001       |
|                       | VLDLNMR average size (nm) | ≤40.6 | 40.7–43.8 | 43.9–47.3 | 47.4–52.0 | >52.0 |
|                       | Model 1    | Referent   | 1.23 (0.96–1.58) | 1.96 (1.56–2.46) | 3.31 (2.68–4.09) | 4.93 (4.06–6.04) | <0.0001     |
|                       | Model 2    | Referent   | 1.25 (0.97–1.62) | 1.67 (1.32–2.10) | 2.22 (1.78–2.76) | 2.80 (2.27–3.46) | <0.0001     |

Data are adjusted HR (95% CI) and (ranges minimum–maximum) and are given for each quintile. See Table 2 legend for model adjustments.

**Incremental value of NMR lipoproteins.** Since NMR lipoproteins are correlated with standard lipids, in particular HDL cholesterol and triglycerides, we performed Cox models that adjusted for triglycerides and HDL and LDL cholesterol in addition to the nonlipid (model 2) risk factors. Although the associations were attenuated, smaller particle size for LDLNMR and HDLNMR remained significant (quintile 1 vs. 5, HR 1.79, [95% CI 1.37–2.33] and 2.39 [1.75–3.28], respectively; P for trend <0.001 for both), as did larger VLDLNMR particle size (quintile 5 vs. 1, 2.04 [1.63–2.56]; P for trend <0.001). The change in the likelihood ratio $\chi^2$ tests was significant for adding either LDLNMR, HDLNMR, or VLDLNMR particle size to models that already included standard lipids and nonlipid risk factors (change in $\chi^2$ 24.53, 48.56, and 59.51, respectively; $P < 0.0001$ for all three).
positive association noted previously in relation to incident CVD in this population of women (23).

Risk factors for type 2 diabetes may differ from those for CVD (24). For CVD risk, we reported that both small and large LDL\textsubscript{NMR} particles had similar increase in risk, which contrasts with the inverse association of large LDL\textsubscript{NMR} and positive association of small LDL\textsubscript{NMR} with risk of diabetes in the current study. For CVD events, NMR lipoprotein profiles in this cohort of women were comparable but not superior to standard lipids, as recently reported (23). This is in contrast to the current findings for type 2 diabetes, where NMR-measured lipoprotein classification by size provided additive and independent risk information to standard lipids and other risk factors.

For HDL particles, the inverse association of HDL\textsubscript{NMR} size with risk of type 2 diabetes was also noted previously in relation to risk of CVD in this population of women (23). Of the HDL\textsubscript{NMR} particles, only large particles were associated with lower risk of diabetes, to a magnitude similar to the association of HDL cholesterol with diabetes, while small particles carried higher risk. Furthermore, adjusting for HDL cholesterol and other risk factors attenuated the association, but larger HDL\textsubscript{NMR} size remained associated with more than twofold increased risk. Previous studies have found strong inverse relationships between insulin resistance and the large HDL\textsubscript{NMR} subclass as measured by NMR (9,10,14) or the corresponding HDL\textsubscript{2} subclass as measured by ultracentrifugation (25).

For VLDL particles, large particles had a greater magnitude of association with diabetes compared with smaller particles, which we explain by large VLDL carrying more triglycerides than small VLDL and correlating more with the severity of insulin resistance (9). Hepatic overproduction of large VLDL particles is a key feature of the dyslipoproteinemia of insulin resistance and type 2 diabetes, with evidence for independent regulation of large and small VLDL particles (26).

In addition, our finding of similar lipoprotein associations with diabetes both early and late in follow-up suggests that these lipoprotein alternations may occur years before the onset of overt hyperglycemia and clinical diagnosis of diabetes, providing a potential opportunity for the early detection and prevention of type 2 diabetes and its complications.

This study has potential limitations. Several of the risk factors were assessed by self-report. Since our study is largely limited to Caucasian women, these data may not be generalizable to men or other patient groups. We studied an apparently healthy cohort at low overall risk for diabetes. While our study found incremental
predictive information for NMR lipoproteins, further studies should be performed in the appropriate patient settings to determine whether a strategy using NMR lipoprotein testing is cost-effective for prevention of type 2 diabetes and related metabolic disorders. Undetected diabetes at study entry is unlikely to have biased our results, since we excluded women with baseline A1C levels ≥6.5% from our primary sample and found similar results when we excluded those with A1C ≥6.0%. In addition, similar results during the first 6 years of follow-up compared with the second 6 years.

We conclude that the size and concentration of NMR-measured LDL, HDL, and VLDL particles were associated with clinical type 2 diabetes, independent of other risk factors, particularly chemically measured HDL cholesterol and triglycerides. The associations of LDL_NMR and HDL_NMR particles with diabetes differed according to size, with larger particles carrying lower risk and smaller particles carrying higher risk. For VLDL_NMR, large particles were associated with higher risk. LDL_NMR, HDL_NMR, and VLDL_NMR particle size remained significant in models that already included standard lipids and risk factors, adding incremental risk information beyond that obtained from established risk factors for type 2 diabetes.

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