Table 2 **Age- and sex-adjusted incidence and adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes according to glucose tolerance status defined by WHO criteria**

| Glucose tolerance level | Person-years at risk, n | No. of events, n | Age- and sex-adjusted incidence | Crude HR (95% CI) | p | Age- and sex-adjusted HR (95% CI) | p | Multivariable-adjusted[a] HR (95% CI) | p |
|---|---|---|---|---|---|---|---|---|---|
| **All-cause dementia** | | | | | | | | | |
| Normal | 6,658 | 115 | 20.1 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| IFG | 854 | 13 | 16.0 | 0.89 (0.50-1.58) | 0.70 | 0.74 (0.42-1.31) | 0.30 | 0.63 (0.35-1.13) | 0.12 |
| IGT | 2,611 | 63 | 24.9 | 1.46 (1.07-1.99) | 0.02 | 1.40 (1.03-1.91) | 0.03 | 1.35 (0.98-1.86) | 0.07 |
| DM | 1,544 | 41 | 29.3 | 1.62 (1.14-2.32) | 0.008 | 1.71 (1.19-2.44) | 0.003 | 1.74 (1.19-2.53) | 0.004 |
| IGT + DM | 4,155 | 104 | 26.3 | 1.52 (1.17-1.98) | 0.002 | 1.51 (1.16-1.97) | 0.002 | 1.46 (1.10-1.92) | 0.008 |
| **Alzheimer disease** | | | | | | | | | |
| Normal | 6,658 | 51 | 8.6 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| IFG | 854 | 5 | 6.6 | 0.77 (0.31-1.94) | 0.58 | 0.63 (0.25-1.57) | 0.32 | 0.61 (0.24-1.55) | 0.29 |
| IGT | 2,611 | 29 | 11.7 | 1.53 (0.97-2.41) | 0.07 | 1.46 (0.92-2.30) | 0.11 | 1.60 (0.99-2.59) | 0.05 |
| DM | 1,544 | 20 | 14.2 | 1.81 (1.08-3.03) | 0.03 | 1.94 (1.16-3.26) | 0.01 | 2.05 (1.18-3.57) | 0.01 |
| IGT + DM | 4,155 | 49 | 12.5 | 1.63 (1.10-2.41) | 0.01 | 1.62 (1.10-2.40) | 0.02 | 1.73 (1.15-2.60) | 0.009 |
| **Vascular dementia** | | | | | | | | | |
| Normal | 6,658 | 27 | 5.1 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| IFG | 854 | 6 | 7.1 | 1.76 (0.73-4.26) | 0.21 | 1.40 (0.58-3.41) | 0.46 | 1.01 (0.41-2.52) | 0.98 |
| IGT | 2,611 | 20 | 7.8 | 1.95 (1.09-3.47) | 0.02 | 1.86 (1.05-3.32) | 0.04 | 1.39 (0.76-2.54) | 0.29 |
| DM | 1,544 | 12 | 8.7 | 2.00 (1.01-3.95) | 0.04 | 2.07 (1.05-4.09) | 0.04 | 1.82 (0.89-3.71) | 0.09 |
| IGT + DM | 4,155 | 32 | 7.9 | 1.97 (1.18-3.29) | 0.01 | 1.94 (1.16-3.23) | 0.01 | 1.54 (0.90-2.63) | 0.11 |
| **Other dementia** | | | | | | | | | |
| Normal | 6,658 | 37 | 6.4 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| IFG | 854 | 2 | 2.2 | 0.42 (0.10-1.75) | 0.23 | 0.36 (0.09-1.51) | 0.16 | 0.34 (0.08-1.44) | 0.14 |
| IGT | 2,611 | 14 | 5.5 | 0.99 (0.54-1.84) | 0.99 | 0.96 (0.52-1.78) | 0.90 | 0.94 (0.49-1.78) | 0.84 |
| DM | 1,544 | 9 | 6.5 | 1.08 (0.52-2.24) | 0.83 | 1.10 (0.53-2.28) | 0.80 | 1.19 (0.56-2.52) | 0.66 |
| IGT + DM | 4,155 | 23 | 5.8 | 1.03 (0.61-1.73) | 0.92 | 1.01 (0.60-1.70) | 0.97 | 0.97 (0.57-1.67) | 0.91 |

Abbreviations: CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glycemia; IGT = impaired glucose tolerance.

[a] Multivariate adjustment was made for age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.

sex-adjusted incidences and HRs of all-cause dementia, AD, and VaD significantly increased with rising 2-hour PG levels. Compared with those with 2-hour PG levels of <6.7 mmol/L, the age- and sex-adjusted incidences and HRs of all-cause dementia, AD, and VaD were marginally or significantly higher in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L and significantly higher in subjects with 2-hour PG levels of ≥11.1 mmol/L. These associations remained robust even after multivariable adjustment; the risks of all-cause dementia and AD were significantly increased in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L and over, and the risk of VaD was significantly higher in those with 2-hour PG levels of ≥11.1 mmol/L.

Sensitivity analysis in which only definite cases of dementia determined by brain autopsy were used as event cases did not make any material difference in these findings, except with respect to VaD, for which the significant association disappeared, probably due to the few event cases (table 5). When only clinical diagnoses were used for cases with both clinical and neuropathologic diagnoses, the findings were substantially unchanged, though the HRs became slightly lower probably due to the decreased accuracy of diagnosis (tables e-1, e-2, and e-3).

**DISCUSSION** In a long-term prospective study of an elderly Japanese population, we demonstrated that diabetes that was assessed 15 years earlier was a significant risk factor for the development of all-cause dementia, AD, and VaD. Moreover, the risks of developing all-cause dementia and its sub-

Table 3 **Age- and sex-adjusted incidence and adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes according to fasting plasma glucose levels**

| Fasting plasma glucose levels | Person-years at risk, n | No. of events, n | Age- and sex-adjusted incidence | Crude HR (95% CI) | p | Age- and sex-adjusted HR (95% CI) | p | Multivariable-adjusted[a] HR (95% CI) | p |
|---|---|---|---|---|---|---|---|---|---|
| **All-cause dementia** | | | | | | | | | |
| **<5.6** | 5,589 | 101 | 20.7 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **5.6-6.0** | 3,286 | 71 | 25.1 | 1.24 (0.91-1.68) | 0.17 | 1.21 (0.89-1.64) | 0.22 | 1.18 (0.86-1.61) | 0.31 |
| **6.1-6.9** | 1,724 | 39 | 21.6 | 1.13 (0.91-1.91) | 0.14 | 1.13 (0.78-1.64) | 0.52 | 0.96 (0.65-1.41) | 0.82 |
| **≥7.0** | 1,067 | 21 | 22.3 | 1.21 (0.70-1.79) | 0.64 | 1.14 (0.71-1.82) | 0.60 | 1.21 (0.75-1.96) | 0.44 |
| | | | | *p* for trend: 0.23 | | *p* for trend: 0.42 | | *p* for trend: 0.63 | |
| **Alzheimer disease** | | | | | | | | | |
| **<5.6** | 5,589 | 48 | 10.1 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **5.6-6.0** | 3,286 | 30 | 10.3 | 1.11 (0.70-1.74) | 0.67 | 1.14 (0.72-1.80) | 0.58 | 1.11 (0.69-1.77) | 0.68 |
| **6.1-6.9** | 1,724 | 16 | 9.1 | 1.15 (0.65-2.02) | 0.64 | 1.00 (0.57-1.77) | 0.99 | 0.99 (0.49-1.64) | 0.72 |
| **≥7.0** | 1,067 | 11 | 11.9 | 1.23 (0.64-2.37) | 0.53 | 1.29 (0.67-2.48) | 0.45 | 1.41 (0.72-2.76) | 0.32 |
| | | | | *p* for trend: 0.47 | | *p* for trend: 0.56 | | *p* for trend: 0.58 | |
| **Vascular dementia** | | | | | | | | | |
| **<5.6** | 5,589 | 24 | 4.9 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **5.6-6.0** | 3,286 | 19 | 6.7 | 1.38 (0.76-2.52) | 0.29 | 1.29 (0.71-2.36) | 0.41 | 1.19 (0.64-2.19) | 0.58 |
| **6.1-6.9** | 1,724 | 17 | 8.7 | 2.40 (1.29-4.47) | 0.006 | 1.93 (1.03-3.61) | 0.04 | 1.48 (0.77-2.84) | 0.24 |
| **≥7.0** | 1,067 | 5 | 5.2 | 1.12 (0.43-2.93) | 0.82 | 1.10 (0.42-2.89) | 0.84 | 0.99 (0.37-2.69) | 0.99 |
| | | | | *p* for trend: 0.10 | | *p* for trend: 0.19 | | *p* for trend: 0.49 | |
| **Other dementia** | | | | | | | | | |
| **<5.6** | 5,589 | 29 | 5.7 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **5.6-6.0** | 3,286 | 22 | 8.1 | 1.33 (0.76-2.31) | 0.32 | 1.27 (0.73-2.21) | 0.40 | 1.21 (0.68-2.16) | 0.51 |
| **6.1-6.9** | 1,724 | 6 | 3.8 | 0.69 (0.29-1.67) | 0.42 | 0.60 (0.25-1.45) | 0.26 | 0.53 (0.22-1.31) | 0.17 |
| **≥7.0** | 1,067 | 5 | 5.2 | 0.92 (0.36-2.37) | 0.86 | 0.91 (0.35-2.36) | 0.85 | 1.02 (0.39-2.67) | 0.97 |
| | | | | *p* for trend: 0.68 | | *p* for trend: 0.53 | | *p* for trend: 0.52 | |

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariate adjustment was made for age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.

types progressively increased with elevating 2-hour PG levels.

In prior prospective epidemiologic studies, there have been conflicting results regarding the associations between diabetes and incidences of all-cause dementia and AD, while the influence of diabetes on the risk of VaD has been positive in most studies.[1,4–7] Cohort studies in which diabetes was defined by nonfasting blood glucose levels or clinical information did not reveal clear associations of diabetes with the development of all-cause dementia and AD,[4–8] while the risks of dementia and its subtypes significantly increased in diabetes in some studies, most of which defined diabetes using the OGTT.[1–3] The latter findings were in accord with ours. This fact suggests that differences in the methods used to define diabetes lead to a discrepancy in the association between diabetes and the risk of dementia, especially AD, and that an OGTT is essential for the definition of diabetes in epidemiologic studies on the diabetes–dementia association.

In our study, the incidence of VaD was significantly higher in subjects with IGT or diabetes than in those with NGT, but this association disappeared after adjustment for other covariates. This might occur due to the few VaD cases. In addition, since other known cardiovascular risk factors, such as hypertension, obesity, and dyslipidemia, accumulate under a prediabetic or diabetic state, as shown in our data (table 1), IGT and diabetes seem to increase the risk of VaD through mediation of these risk factors, especially hypertension.

In the present study, increased 2-hour PG levels including a prediabetic range were significantly

Table 4 **Age- and sex-adjusted incidence and adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes according to 2-hour postload glucose levels**

| 2-Hour postload glucose levels | Person-years at risk, n | No. of events, n | Age- and sex-adjusted incidence | Crude HR (95% CI) | p | Age- and sex-adjusted HR (95% CI) | p | Multivariable-adjusted[a] HR (95% CI) | p |
|---|---|---|---|---|---|---|---|---|---|
| **All-cause dementia** | | | | | | | | | |
| **<6.7** | 5,354 | 85 | 17.6 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **6.7–7.7** | 2,277 | 44 | 20.9 | 1.20 (0.84–1.73) | 0.32 | 1.25 (0.87–1.80) | 0.24 | 1.16 (0.78–1.71) | 0.47 |
| **7.8–11.0** | 2,844 | 67 | 24.7 | 1.53 (1.11–2.11) | 0.009 | 1.54 (1.12–2.12) | 0.009 | 1.50 (1.07–2.11) | 0.02 |
| **≥11.1** | 1,192 | 36 | 32.8 | 2.08 (1.41–3.07) | <0.001 | 2.32 (1.57–3.44) | <0.001 | 2.47 (1.62–3.77) | <0.001 |
| | | | | *p* for trend: <0.001 | | *p* for trend: <0.001 | | *p* for trend: <0.001 | |
| **Alzheimer disease** | | | | | | | | | |
| **<6.7** | 5,354 | 37 | 7.6 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **6.7–7.7** | 2,277 | 20 | 8.8 | 1.25 (0.73–2.16) | 0.41 | 1.23 (0.71–2.12) | 0.46 | 1.49 (0.83–2.67) | 0.17 |
| **7.8–11.0** | 2,844 | 30 | 11.3 | 1.59 (0.98–2.57) | 0.06 | 1.56 (0.96–2.53) | 0.07 | 1.87 (1.13–3.12) | 0.02 |
| **≥11.1** | 1,192 | 18 | 15.8 | 2.44 (1.39–4.29) | 0.002 | 2.75 (1.56–4.85) | <0.001 | 3.42 (1.83–6.40) | <0.001 |
| | | | | *p* for trend: 0.002 | | *p* for trend: <0.001 | | *p* for trend: <0.001 | |
| **Vascular dementia** | | | | | | | | | |
| **<6.7** | 5,354 | 21 | 4.6 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **6.7–7.7** | 2,277 | 12 | 6.3 | 1.33 (0.65–2.70) | 0.43 | 1.49 (0.73–3.04) | 0.27 | 1.14 (0.54–2.41) | 0.73 |
| **7.8–11.0** | 2,844 | 20 | 7.2 | 1.83 (0.99–3.38) | 0.05 | 1.87 (1.01–3.45) | 0.04 | 1.38 (0.72–2.64) | 0.34 |
| **≥11.1** | 1,192 | 12 | 11.2 | 2.75 (1.35–5.60) | 0.005 | 3.15 (1.55–6.43) | 0.002 | 2.66 (1.24–5.70) | 0.01 |
| | | | | *p* for trend: 0.004 | | *p* for trend: 0.002 | | *p* for trend: 0.02 | |
| **Other dementia** | | | | | | | | | |
| **<6.7** | 5,354 | 27 | 5.4 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| **6.7–7.7** | 2,277 | 12 | 5.8 | 1.04 (0.52–2.04) | 0.92 | 1.08 (0.55–2.15) | 0.82 | 0.86 (0.40–1.84) | 0.70 |
| **7.8–11.0** | 2,844 | 17 | 6.2 | 1.21 (0.66–2.23) | 0.53 | 1.21 (0.66–2.23) | 0.53 | 1.14 (0.60–2.16) | 0.69 |
| **≥11.1** | 1,192 | 6 | 5.8 | 1.05 (0.44–2.55) | 0.91 | 1.12 (0.46–2.71) | 0.81 | 1.21 (0.48–3.04) | 0.69 |
| | | | | *p* for trend: 0.65 | | *p* for trend: 0.59 | | *p* for trend: 0.59 | |

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariate adjustment was made for age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.

linked to elevated risks of all-cause dementia, AD, and VaD, but no such associations were observed for FPG. The epidemiologic evidence from Asia has also indicated that 2-hour PG levels are better in detecting prediabetes and diabetes compared with FPG levels.[19] However, very few prospective studies have investigated the associations between FPG as well as 2-hour PG levels and the risks of dementia and its subtypes. Only the Uppsala Longitudinal Study of Adult Men evaluated the associations of FPG levels with the risks of developing AD and VaD,[20,21] and this study concluded that increased FPG levels were not risk factors for these subtypes of dementia. This is in good agreement with our findings. The Uppsala Study[21] and the Honolulu-Asia Aging Study[1] also found no clear associations between 2-hour PG levels and the risks of AD and VaD. These findings are inconsistent with ours. Our recent clinicopathologic study of deceased Hisayama residents revealed that higher levels of 2-hour PG but not of FPG were clearly associated with increased risk for formation of neuritic plaques even after adjustment for confounding factors.[22] This evidence together with the findings of the present study suggests that elevated 2-hour PG levels play an important role in the formation of neuritic plaques, and thereby in the development of AD. Meanwhile, it is well known that increased 2-hour PG levels are closely associated with the development of stroke, which is well established as a main cause of VaD. Thus, it is reasonable to postulate a close association between 2-hour PG levels and the risk of VaD.

Possible pathophysiologic mechanisms through which diabetes or elevated blood glucose levels might

Table 5 **Age- and sex-adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes determined by autopsy according to 2-hour postload glucose levels**

| 2-Hour postload glucose levels | Person-years at risk, n | No. of events, n | Crude HR (95% CI) | p | Age- and sex-adjusted HR (95% CI) | p |
|---|---|---|---|---|---|---|
| **All-cause dementia** | | | | | | |
| <6.7 | 5,354 | 47 | 1 (referent) | | 1 (referent) | |
| 6.7–7.7 | 2,277 | 23 | 1.14 (0.69–1.88) | 0.61 | 1.24 (0.75–2.05) | 0.39 |
| 7.8–11.0 | 2,844 | 29 | 1.19 (0.75–1.89) | 0.47 | 1.20 (0.76–1.91) | 0.44 |
| ≥11.1 | 1,192 | 19 | 1.94 (1.14–3.31) | 0.01 | 2.24 (1.31–3.83) | 0.003 |
| | | | *p* for trend: 0.04 | | *p* for trend: 0.02 | |
| **Alzheimer disease** | | | | | | |
| <6.7 | 5,354 | 12 | 1 (referent) | | 1 (referent) | |
| 6.7–7.7 | 2,277 | 7 | 1.35 (0.53–3.44) | 0.53 | 1.40 (0.55–3.56) | 0.48 |
| 7.8–11.0 | 2,844 | 12 | 1.94 (0.87–4.33) | 0.10 | 1.92 (0.86–4.26) | 0.11 |
| ≥11.1 | 1,225 | 8 | 3.27 (1.34–8.00) | 0.009 | 3.88 (1.58–9.53) | 0.003 |
| | | | *p* for trend: 0.009 | | *p* for trend: 0.005 | |
| **Vascular dementia** | | | | | | |
| <6.7 | 5,354 | 17 | 1 (referent) | | 1 (referent) | |
| 6.7–7.7 | 2,277 | 8 | 1.09 (0.47–2.54) | 0.83 | 1.23 (0.53–2.86) | 0.63 |
| 7.8–11.0 | 2,844 | 8 | 0.90 (0.39–2.09) | 0.81 | 0.92 (0.40–2.12) | 0.84 |
| ≥11.1 | 1,192 | 7 | 1.98 (0.82–4.77) | 0.13 | 2.32 (0.96–5.61) | 0.06 |
| | | | *p* for trend: 0.36 | | *p* for trend: 0.26 | |
| **Other dementia** | | | | | | |
| <6.7 | 5,354 | 18 | 1 (referent) | | 1 (referent) | |
| 6.7–7.7 | 2,277 | 8 | 1.04 (0.45–2.39) | 0.93 | 1.17 (0.51–2.70) | 0.72 |
| 7.8–11.0 | 2,844 | 9 | 0.96 (0.43–2.14) | 0.92 | 0.98 (0.44–2.19) | 0.97 |
| ≥11.1 | 1,192 | 4 | 1.04 (0.35–3.07) | 0.95 | 1.16 (0.39–3.43) | 0.79 |
| | | | *p* for trend: 0.99 | | *p* for trend: 0.88 | |

Abbreviations: CI = confidence interval; HR = hazard ratio.

affect the initiation and promotion of dementia have been extensively discussed in a number of studies.[23] A recent review summarized 4 major pathways for hyperglycemia-induced dementia: namely, atherosclerosis, microvascular disease, glucose toxicity leading to the accumulation of advanced protein glycation and increased oxidative stress, and changes in insulin metabolism resulting in an insulin-resistant state and distorted amyloid metabolism in the brain.[23] The former 2 pathways are considered to be involved in the development of VaD, while the latter 2 pathways may mainly contribute to the development of AD. Additionally, recent evidence has emerged to imply that vascular factors may be involved in AD.[23] It is reported that 2-hour PG values can be a good marker of oxidative stress levels arising from hyperglycemia[24,25] and correlate with insulin resistance.[26] Higher oxidative stress and insulin resistance may precede the accumulation of amyloid-$\beta$ peptide and neurofibrillary tangles[23,27] and accelerate arteriosclerosis in the brain,[28] resulting in increased risk of AD and VaD. It is known that Asians have lower levels of insulin secretion compared with other ethnic groups[29] and can develop diabetes, insulin resistance, and metabolic syndrome with lower body mass index levels.[30] These findings suggest that hyperglycemia plays a larger role in the development of dementia compared with insulin resistance in Asians including Japanese. Further studies are needed to elucidate the pathogenesis of hyperglycemia and diabetes in the development of dementia.

The strengths of our study include its longitudinal population-based study design, use of OGTT for determination of glucose tolerance levels in all subjects, long duration of follow-up, perfect follow-up of subjects, and morphologic examination of the brains of most dementia cases with autopsy and neuroimaging. Several limitations of our study should be noted. First, the diagnosis of glucose tolerance status was based on a single measurement of glucose levels at baseline, as was the case in most other epidemiologic studies. During the follow-up, risk factor levels were changed due to modifications in lifestyle or medication especially in subjects with diabetes, and

misclassification of glucose tolerance categories was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown here. Second, some subjects (n = 33 to 65) did not participate in the follow-up surveys of cognitive function performed in 1992, 1998, and 2005, and their cognitive conditions were evaluated only by mail or telephone. This might have resulted in failure to detect dementia cases. However, we also collected information on the development of dementia in another way, namely through the daily monitoring system established in the town. Thus, we believe that we detected almost all dementia cases, and this bias did not affect our findings. Third, the diagnosis of dementia was verified by autopsy only in 50.9% of dementia cases, resulting in a certain degree of subtype misclassification; agreement rate between clinical diagnosis and neuropathologic diagnosis was not high (64.4%) in our autopsy cases of dementia. However, a sensitivity analysis using only definite cases of dementia determined by brain autopsy did not make any material difference in our findings.

Our findings emphasize the need to consider diabetes as a potential risk factor for all-cause dementia, AD, and probably VaD. The other main finding, that elevated 2-hour PG levels are closely associated with increased risks of all-cause dementia and its subtypes, supports the view that postprandial glucose regulation is critical to prevent future dementia. Further investigations are required to clarify the associations between 2-hour PG levels by the OGTT and subtypes of dementia in other ethnic populations.

## AUTHOR CONTRIBUTIONS

Tomoyuki Ohara contributed to the study concept, design, data collection, endpoint adjudication, interpretation of data, statistical analysis, and writing the manuscript. Yasufumi Doi contributed to the study concept, design, interpretation of data, statistical analysis, and writing the manuscript. Toshiharu Ninomiya contributed to the data collection, endpoint adjudication, interpretation of data, and statistical analysis. Yoichiro Hirakawa and Jun Hata contributed to data collection and interpretation of data. Toru Iwaki and Shigenobu Kanba contributed to endpoint adjudication and interpretation of data. Yutaka Kiyohara is a study coordinator and contributed to the study performance, obtaining supporting sources, study concept, design, endpoint adjudication, interpretation of data, and writing of manuscript. All authors critically reviewed the manuscript and approved final version.

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## DISCLOSURE

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# Midlife and Late-Life Blood Pressure and Dementia in Japanese Elderly

## The Hisayama Study

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*Abstract*—The associations between blood pressure and dementia have been inconclusive. We followed up a total of 668 community-dwelling Japanese individuals without dementia, aged 65 to 79 years, for 17 years and examined the associations of late-life and midlife hypertension with the risk of vascular dementia and Alzheimer disease using the Cox proportional hazards model. During the follow-up, 76 subjects experienced vascular dementia and 123 developed Alzheimer disease. The age- and sex-adjusted incidence of vascular dementia significantly increased with elevated late-life blood pressure levels (normal: 2.3, prehypertension: 8.4, stage 1 hypertension: 12.6, and stage 2 hypertension: 18.9 per 1000 person-years; $P_{trend}<0.001$), whereas no such association was observed for Alzheimer disease ($P_{trend}=0.88$). After adjusting for potential confounding factors, subjects with prehypertension and stage 1 or stage 2 hypertension had 3.0-fold, 4.5-fold, and 5.6-fold greater risk of vascular dementia, respectively, compared with subjects with normal blood pressure. Likewise, there was a positive association of midlife blood pressure levels with the risk of vascular dementia but not with the risk of Alzheimer disease. Compared with those without hypertension in both midlife and late life, subjects with midlife hypertension had an ≈5-fold greater risk of vascular dementia, regardless of late-life blood pressure levels. Our findings suggest that midlife hypertension and late-life hypertension are significant risk factors for the late-life onset of vascular dementia but not for that of Alzheimer disease in a general Japanese population. Midlife hypertension is especially strongly associated with a greater risk of vascular dementia, regardless of late-life blood pressure levels. (***Hypertension.* 2011;58:22-28.**) • **Online Data Supplement**

**Key Words:** prospective studies ■ aged ■ hypertension ■ vascular dementia ■ Alzheimer disease

Vascular dementia (VaD) has been acknowledged to be more prevalent in Japan as compared with Western countries.[1–5] We reported previously that the prevalence of VaD did not apparently decrease over the past 2 decades,[2] despite the fact that the incidence of stroke significantly decreased because of the improvement of blood pressure (BP) lowering therapy since the 1970s.[6] In addition, the incidence of Alzheimer disease (AD) in Japanese studies is greater to almost same degree as that of Western studies in recent years,[1,4,5] resulting in a drastic increase in the burden of dementia in Japan.[2]

Hypertension and dementia are common disorders in the elderly.[7,8] Because hypertension has been shown to be a major risk factor for cerebrovascular disease, higher BP was likely to be strongly associated with a greater risk of VaD.[9] In addition, recent evidence has emerged to imply that vascular factors may be involved in AD, which has traditionally been considered a primarily neurodegenerative disorder.[10,11] However, the results of observational longitudinal studies showing the effects of BP on the risks of dementia and its subtypes are inconsistent.[12,13] In particular, some studies have suggested that midlife hypertension is a risk factor for late-life dementia, whereas lower diastolic BP in late life may be related to increased risks of dementia and AD.[12] These facts raise the possibilities that the effects of hypertension on the development of dementia may be different between midlife and late life, possibly because the longitudinal changes related to hypertension in the brain may begin earlier in the adult life span.[12,13] However, few studies have compared the effects of midlife and late-life hypertension on the development of dementia in an identical population.

The purposes of this study were to investigate the association of BP levels in midlife and late life with the development of dementia and its subtypes in a general Japanese population and to elucidate whether the effects of hypertension on the risk of dementia are different between midlife and late life in an identical population. The findings from this study are expected to provide clear evidence of the diverse

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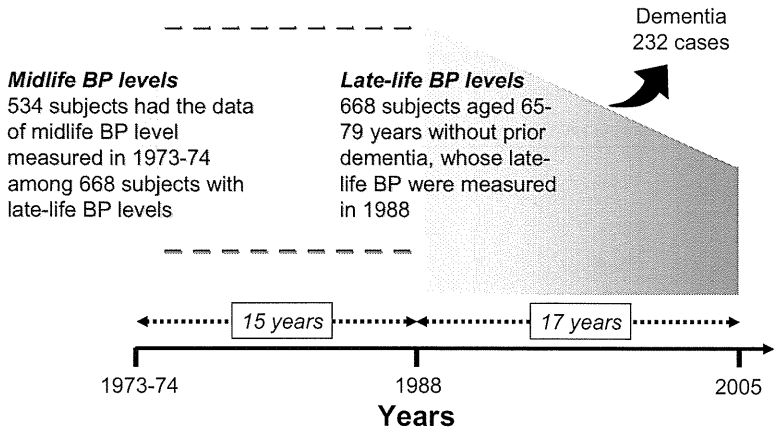


**Figure.** Diagram of the study design. BP indicates blood pressure.

associations of BP levels with the risk of dementia in midlife and late life.

## Methods

### Study Population

A population-based prospective study of cerebro-cardiovascular diseases was established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. Full community surveys of health status and neurological conditions of the residents aged ≥40 years have been repeated since 1961.[6] In addition, comprehensive surveys of cognitive function in the elderly, including neuropsychological tests, have been conducted every 6 or 7 years since 1985.[2]

In 1988, a total of 682 residents aged 65 to 79 years (90.5% of the total population in this age group) participated in a health checkup. After excluding 12 subjects with dementia at baseline and 2 subjects who died before starting the follow-up, the remaining 668 subjects (266 men and 402 women) were enrolled in this study to investigate the association between late-life BP and the risk of dementia. Among them, 534 subjects (210 men and 324 women) had also participated in a health checkup conducted in 1973–1974 and were included in the analysis of the effects of midlife BP on the risk of late-life dementia (Figure). Written, informed consent was obtained from the participants at baseline in 1988. This study was conducted with the approval of the ethics committee of the Kyushu University Faculty of Medicine.

### BP Categories

Sitting BP was measured with a sphygmomanometer 3 times at the right upper arm after ≥5 minutes of rest, and the mean of the 3 measurements was used in the analysis. BP levels measured in 1973–1974 and 1988 were classified into 4 categories according to the criteria of the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).[14]

The extended Materials and Methods section provides detailed information on the follow-up survey, diagnosis of dementia, other risk factors, and statistical analysis. Please see the online Data Supplement at http://hyper.ahajournals.org.

## Results

The clinical characteristics of the study population according to BP levels defined by the criteria of JNC-7 in late life (1988) are summarized in the top part of Table 1. The mean age of the overall population was 72±4 years old. Subjects with higher BP levels were likely to be older. The proportion of subjects using antihypertensive agents and the proportion with diabetes mellitus increased gradually with higher BP levels. There were no associations of BP levels with the mean serum total cholesterol levels and the proportion of women, educational status, or smoking habit. Likewise, the clinical characteristics according to BP levels at midlife (1973–1974) are shown in the bottom part of Table 1. The mean age at midlife was 57±4 years old. The mean values of age, serum total cholesterol, and body mass index and the proportion of the use of antihypertensive agents increased with higher midlife BP levels.

During the 17-year follow-up period, 232 subjects developed dementia of some kind. Of these, 199 (85.8%) underwent evaluation with neuroimaging, and 115 (49.6%) received a general autopsy examination; in 106 cases, both were performed. Thus, 208 subjects in all (89.7%) had some kind of morphological examination. Among dementia cases, 15 AD cases and 13 VaD cases had other coexisting subtypes of dementia, of which 8 cases were a mixed type of AD and VaD. These cases were counted as events in the analysis for each subtype. In all, 123 subjects developed AD, and 76 developed VaD.

First, we estimated the associations between late-life BP levels defined by the criteria of JNC-7 and the risk of dementia (Table 2 and Figure S1, available in the online Data Supplement at http://hyper.ahajournals.org). The age- and sex-adjusted incidence of all-cause dementia showed an increasing linear trend with the rise of late-life BP levels ($P_{trend}$=0.07). In regard to subtypes of dementia, the age- and sex-adjusted incidence of VaD significantly increased with elevated late-life BP levels ($P_{trend}$<0.001). Meanwhile, there were no significant associations between late-life BP levels and the age- and sex-adjusted incidence of AD ($P_{trend}$=0.88). Table 2 also shows the multivariate-adjusted hazard ratios of all-cause dementia and its subtypes across late-life BP levels defined by the criteria of JNC-7. After adjusting for potential confounding factors (age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake), the risk of VaD increased progressively with elevated BP levels. This relationship was not altered substantially after adjusting for the above-mentioned confounding factors and serum homocysteine. No clear associations were observed between BP levels and the risks of all-cause dementia and AD. There was no evidence of heterogeneity in these associations between the

**Table 1. Clinical Characteristics of Study Population**

| Characteristics | Blood Pressure Levels Defined by JNC-7 | | | | *P* for Trend |
|---|---|---|---|---|---|
| | Normal | Prehypertension | Stage 1 Hypertension | Stage 2 Hypertension | |
| Risk factors according to blood pressure levels in 1988 | | | | | |
| No. of participants | 106 | 227 | 200 | 135 | |
| Age, mean (SD), y | 71 (4) | 71 (4) | 73 (4) | 73 (4) | <0.001 |
| Women, % | 54.7 | 63.9 | 57.0 | 63.0 | 0.58 |
| Educational status, % | | | | | |
| ≤6 y | 11.3 | 12.1 | 18.6 | 13.6 | 0.06* |
| 7 to 9 y | 50.9 | 64.1 | 54.3 | 57.6 | |
| ≥10 y | 37.8 | 23.8 | 27.1 | 28.8 | |
| Systolic blood pressure, mean (SD), mm Hg | 109 (8) | 130 (6) | 149 (6) | 177 (17) | <0.001 |
| Diastolic blood pressure, mean (SD), mm Hg | 65 (7) | 72 (8) | 79 (9) | 84 (11) | <0.001 |
| Antihypertensive agents, % | 3.8 | 22.0 | 34.0 | 51.1 | <0.001 |
| Diabetes mellitus, % | 4.7 | 13.7 | 12.0 | 25.9 | <0.001 |
| Chronic kidney disease, % | 8.5 | 15.9 | 16.5 | 25.4 | 0.001 |
| Serum total cholesterol, mean (SD), mmol/L | 5.1 (1.1) | 5.5 (1.1) | 5.3 (1.1) | 5.4 (1.2) | 0.24 |
| Body mass index, mean (SD), kg/m$^2$ | 20.4 (2.5) | 22.2 (2.9) | 22.3 (3.1) | 23.2 (3.7) | <0.001 |
| Serum homocysteine, mean (SD), $\mu$mol/L | 9.4 (4.0) | 9.4 (3.4) | 10.5 (7.4) | 10.8 (5.9) | 0.01 |
| History of stroke, % | 1.9 | 4.4 | 7.5 | 9.6 | 0.005 |
| Smoking habits, % | 25.5 | 17.2 | 20.0 | 20.7 | 0.69 |
| Alcohol intake, % | 16.0 | 21.1 | 24.6 | 30.4 | 0.006 |
| Risk factors according to blood pressure levels in 1973–1974 | | | | | |
| No. of participants | 122 | 185 | 153 | 74 | |
| Age, mean (SD), y | 56 (4) | 57 (4) | 58 (4) | 58 (4) | <0.001 |
| Women, % | 57.4 | 60.0 | 58.2 | 73.0 | 0.10 |
| Educational status, % | | | | | |
| ≤6 y | 8.2 | 13.0 | 17.0 | 18.9 | 0.24* |
| 7 to 9 y | 69.7 | 60.0 | 60.1 | 58.1 | |
| ≥10 y | 22.1 | 27.0 | 22.9 | 23.0 | |
| Systolic blood pressure, mean (SD), mm Hg | 109 (7) | 129 (7) | 147 (7) | 178 (16) | <0.001 |
| Diastolic blood pressure, mean (SD), mm Hg | 67 (6) | 76 (7) | 85 (7) | 94 (11) | <0.001 |
| Antihypertensive agents, % | 0.0 | 2.7 | 12.4 | 20.3 | <0.001 |
| Diabetes mellitus, % | 0.8 | 0.5 | 3.9 | 1.4 | 0.18 |
| Chronic kidney disease, % | 3.3 | 1.7 | 3.9 | 4.1 | 0.49 |
| Serum total cholesterol, mmol/L, mean (SD) | 4.9 (0.8) | 4.9 (0.8) | 5.0 (0.8) | 5.2 (0.8) | 0.03 |
| Body mass index, mean (SD), kg/m$^2$ | 21.4 (2.6) | 22.2 (2.7) | 22.8 (3.0) | 23.2 (4) | <0.001 |
| History of stroke, % | 0.0 | 0.0 | 1.3 | 1.4 | 0.11 |
| Smoking habits, % | 36.1 | 35.1 | 30.1 | 29.7 | 0.21 |
| Alcohol intake, % | 20.5 | 28.1 | 34.0 | 25.7 | 0.13 |

JNC-7 indicates the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
*Educational status was tested by using $\chi^2$ test.

sexes and between subjects with or without antihypertensive agents (all $P_{heterogeneity}>0.10$).

Likewise, we investigated the associations between midlife BP levels defined by the criteria of JNC-7 and the risk of dementia developing in late life. Greater midlife BP levels were associated linearly with the increased risk of VaD but not AD (Table 3). Reflecting the rising risk of VaD, there was an increasing linear trend in the risk of all-cause dementia with higher BP levels in midlife. Sensitivity analyses, in which the all of the event cases were definite cases of dementia as determined by brain autopsy, did not make any material differences in these findings (Table S1).

In addition, we examined the effects of systolic BP and diastolic BP levels measured in late life and in midlife on the risk of incident VaD (Figure S2). In multivariate analysis, the risk of VaD significantly increased with elevated systolic BP

**Table 2. Association Between Late-Life Blood Pressure and the Risk of Dementia During 17-Y Follow-Up**

| Late-Life BP Levels Defined by JNC-7 | No. of Events | No. of Participants | Age- and Sex-Adjusted Incidence, per $10^3$ PYs (95% CI) | Age-, Sex-, and Education-Adjusted HR (95% CI) | *P* | Multivariable-Adjusted (Model A)* HR (95% CI) | *P* | Multivariable-Adjusted (Model B)† HR (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|---|
| All-cause dementia | | | | | | | | | |
| Normal | 33 | 106 | 28.0 (17.9 to 38.1) | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Prehypertension | 71 | 227 | 27.9 (21.2 to 34.5) | 0.86 (0.57 to 1.31) | 0.49 | 0.84 (0.54 to 1.29) | 0.42 | 0.89 (0.57 to 1.39) | 0.60 |
| Stage 1 hypertension | 75 | 200 | 32.0 (24.8 to 39.3) | 1.07 (0.71 to 1.63) | 0.73 | 1.08 (0.69 to 1.68) | 0.74 | 1.12 (0.71 to 1.79) | 0.62 |
| Stage 2 hypertension | 53 | 135 | 37.4 (27.4 to 47.5) | 1.28 (0.82 to 1.98) | 0.28 | 1.12 (0.68 to 1.87) | 0.65 | 1.16 (0.68 to 1.98) | 0.59 |
| *P* for trend | | | 0.07 | 0.09 | | 0.25 | | 0.29 | |
| Vascular dementia | | | | | | | | | |
| Normal | 2 | 106 | 2.3 (−0.9 to 5.4) | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Prehypertension | 19 | 227 | 8.4 (4.6 to 12.3) | 3.91 (0.91 to 16.85) | 0.07 | 3.01 (0.68 to 13.31) | 0.15 | 3.20 (0.71 to 14.36) | 0.13 |
| Stage 1 hypertension | 29 | 200 | 12.6 (8.0 to 17.2) | 6.46 (1.53 to 27.21) | 0.01 | 4.46 (1.02 to 19.42) | 0.046 | 4.72 (1.05 to 21.28) | 0.04 |
| Stage 2 hypertension | 26 | 135 | 18.9 (11.6 to 26.3) | 9.98 (2.35 to 42.35) | 0.002 | 5.57 (1.22 to 25.49) | 0.03 | 7.26 (1.54 to 34.17) | 0.01 |
| *P* for trend | | | <0.001 | <0.001 | | 0.009 | | 0.003 | |
| Alzheimer disease | | | | | | | | | |
| Normal | 22 | 106 | 17.9 (9.8 to 26.0) | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| Prehypertension | 39 | 227 | 14.0 (9.4 to 18.6) | 0.71 (0.42 to 1.20) | 0.20 | 0.73 (0.42 to 1.27) | 0.27 | 0.74 (0.42 to 1.27) | 0.27 |
| Stage 1 hypertension | 39 | 200 | 16.8 (11.5 to 22.0) | 0.86 (0.51 to 1.47) | 0.58 | 0.95 (0.54 to 1.68) | 0.87 | 0.93 (0.52 to 1.65) | 0.80 |
| Stage 2 hypertension | 23 | 135 | 14.7 (8.7 to 20.7) | 0.84 (0.46 to 1.52) | 0.56 | 0.84 (0.42 to 1.66) | 0.61 | 0.67 (0.33 to 1.37) | 0.27 |
| *P* for trend | | | 0.88 | 0.92 | | 0.97 | | 0.55 | |

BP indicates blood pressure; HR, hazard ratio; PYs, person-years; JNC-7, the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

*Model A was adjusted for potential confounding covariates in late life, namely, age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

†Model B was adjusted for potential confounding covariates included in model 1 plus serum homocysteine.

levels in both late life ($P_{trend}$=0.0100) and midlife ($P_{trend}$<0.0001). Every 10-mm Hg increment in systolic BP in late life and midlife was associated with an 18% (95% CI: 7% to 31%) and a 24% (95% CI: 12% to 37%) higher risk of incident VaD, respectively. Such an association was also seen for diastolic BP levels in midlife ($P_{trend}$=0.001) but not for diastolic late-life BP levels ($P_{trend}$=0.60). The risk of VaD increased by 37% (95% CI: 9% to 72%) per 10-mm Hg increment in midlife diastolic BP. When we divided the systolic BP category of <120 mm Hg or the diastolic BP category of <80 mm Hg into 2 categories of <110 and 110 to 119 mm Hg or <70 and 70 to 79 mm Hg, respectively, the subjects with the lowest systolic or diastolic BP level did not have a greater risk of VaD than those with second-lowest systolic or diastolic BP level (Table S2). There was no evidence of linear or J-curve associations of systolic BP and diastolic BP levels in late life or in midlife with the risks of AD (Table S2).

Finally, we estimated the effect of the change in BP levels from midlife to late life on the risk of the development of dementia (Table 4). Compared with those having BP levels of <140/90 mm Hg in both midlife and late life, subjects with BP levels of <140/90 mm Hg in midlife and ≥140/90 mm Hg in late life had a 3.32-fold greater risk of VaD after adjusting for potential confounding factors, whereas subjects with midlife BP levels of ≥140/90 mm Hg had an ≈5-fold greater risk of VaD, regardless of late-life BP levels. Reflecting the increasing risk of VaD, the risk of all-cause dementia tended to be greater in subjects with midlife BP levels of ≥140/90 mm Hg. There was no clear association of any elevation in BP levels with the risk of AD.

## Discussion

In the present study, we demonstrated a clear association of higher BP levels in both midlife and late life with a greater risk of the development of VaD, whereas such associations were not observed for AD. Intriguingly, subjects with higher BP levels in midlife were at increasing risks of late-life onset of all-cause dementia and VaD, regardless of late-life BP levels. These findings lend support to the hypothesis that the vascular damages related to hypertension in the brain begin earlier in the life span and are gradually becoming less reversible.[12,13] Therefore, it would be reasonable to suppose that the optimal control of midlife BP levels is clinically important to reduce the risk of late-life dementia in the general Japanese population.

Several prospective studies have examined the association between late-life BP and incident dementia, but the findings have been inconsistent.[12,15–22] Several cohort studies failed to reveal a significant association between higher late-life BP and the risk of all-cause dementia or AD,[16–19] whereas other studies reported a positive association with VaD.[15,16] Our findings were comparable with the latter. In contrast, a few studies have reported that lower late-life BP predisposed elderly subjects, especially those aged ≥80 years, to all-cause dementia or AD.[20–22] In a randomized control trial conducted

**Table 3. Association Between Midlife Blood Pressure and the Risk of Dementia in Late Life**

| Midlife BP Levels Defined by JNC-7 | No. of Events | No. of Participants | Age-, Sex-, and Education-Adjusted | | Multivariable-Adjusted* | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* | HR (95% CI) | *P* |
| All-cause dementia | | | | | | |
| Normal | 38 | 122 | 1.00 (reference) | | 1.00 (reference) | |
| Prehypertension | 56 | 185 | 0.92 (0.60 to 1.40) | 0.68 | 0.92 (0.60 to 1.41) | 0.71 |
| Stage 1 hypertension | 66 | 153 | 1.51 (1.00 to 2.29) | 0.05 | 1.73 (1.12 to 2.65) | 0.01 |
| Stage 2 hypertension | 33 | 74 | 1.79 (1.11 to 2.90) | 0.02 | 1.95 (1.18 to 3.24) | 0.01 |
| *P* for trend | | | 0.001 | | <0.001 | |
| Vascular dementia | | | | | | |
| Normal | 4 | 122 | 1.00 (reference) | | 1.00 (reference) | |
| Prehypertension | 15 | 185 | 2.29 (0.75 to 6.99) | 0.15 | 2.38 (0.77 to 7.30) | 0.13 |
| Stage 1 hypertension | 26 | 153 | 5.12 (1.76 to 14.93) | 0.003 | 5.96 (2.00 to 17.77) | 0.001 |
| Stage 2 hypertension | 18 | 74 | 8.92 (2.95 to 26.93) | <0.001 | 10.07 (3.25 to 31.25) | <0.001 |
| *P* for trend | | | <0.001 | | <0.001 | |
| Alzheimer disease | | | | | | |
| Normal | 26 | 122 | 1.00 (reference) | | 1.00 (reference) | |
| Prehypertension | 33 | 185 | 0.80 (0.47 to 1.35) | 0.4 | 0.77 (0.45 to 1.31) | 0.34 |
| Stage 1 hypertension | 31 | 153 | 1.09 (0.63 to 1.87) | 0.76 | 1.26 (0.72 to 2.21) | 0.42 |
| Stage 2 hypertension | 12 | 74 | 0.97 (0.48 to 1.96) | 0.94 | 1.05 (0.50 to 2.22) | 0.89 |
| *P* for trend | | | 0.72 | | 0.45 | |

BP indicates blood pressure; HR, hazard ratio; JNC-7, the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

*Data were adjusted for potential confounding covariates in late life, namely, age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

in the very elderly, BP lowering did not increase the risk of dementia, but the BP levels achieved in the intervention group were still >140/90 mm Hg.[23] Therefore, BP lowering for very elderly people may be implemented with caution. To date, it might be said that there is no strong evidence to indicate that elevated late-life BP is a risk factor for dementia.

Several longitudinal studies have examined the associations between midlife BP and the risk of dementia.[24–28] The

**Table 4. Effects of Change in Blood Pressure Levels From Midlife to Late Life on the Risk of Dementia**

| BP Levels, mm Hg | | | No. of Events | No. of Participants | Percentage of Use of Antihypertensive Agents | | Age-, Sex-, and Education-Adjusted | | Multivariable-Adjusted* | |
|---|---|---|---|---|---|---|---|---|---|---|
| Midlife | | Late-Life | | | Midlife | Late-Life | HR (95% CI) | *P* | HR (95% CI) | *P* |
| All-cause dementia | | | | | | | | | | |
| <140/90 | → | <140/90 | 59 | 197 | 0.5 | 9.2 | 1.00 (reference) | | 1.00 (reference) | |
| <140/90 | → | ≥140/90 | 35 | 110 | 3.6 | 21.8 | 1.05 (0.69 to 1.61) | 0.81 | 1.13 (0.73 to 1.75) | 0.58 |
| ≥140/90 | → | <140/90 | 35 | 78 | 10.3 | 42.3 | 1.74 (1.14 to 2.66) | 0.01 | 1.88 (1.19 to 2.96) | 0.007 |
| ≥140/90 | → | ≥140/90 | 64 | 149 | 17.5 | 55.0 | 1.68 (1.17 to 2.42) | 0.005 | 1.64 (1.09 to 2.46) | 0.02 |
| Vascular dementia | | | | | | | | | | |
| <140/90 | → | <140/90 | 6 | 197 | 0.5 | 9.2 | 1.00 (reference) | | 1.00 (reference) | |
| <140/90 | → | ≥140/90 | 13 | 110 | 3.6 | 21.8 | 3.71 (1.40 to 9.83) | 0.008 | 3.29 (1.21 to 8.94) | 0.02 |
| ≥140/90 | → | <140/90 | 14 | 78 | 10.3 | 42.3 | 6.68 (2.55 to 17.52) | <0.001 | 5.32 (1.9 to 14.89) | 0.001 |
| ≥140/90 | → | ≥140/90 | 30 | 149 | 17.5 | 55.0 | 6.94 (2.86 to 16.88) | <0.001 | 4.72 (1.83 to 12.17) | 0.001 |
| Alzheimer disease | | | | | | | | | | |
| <140/90 | → | <140/90 | 41 | 197 | 0.5 | 9.2 | 1.00 (reference) | | 1.00 (reference) | |
| <140/90 | → | ≥140/90 | 18 | 110 | 3.6 | 21.8 | 0.79 (0.45 to 1.39) | 0.41 | 0.91 (0.51 to 1.62) | 0.74 |
| ≥140/90 | → | <140/90 | 14 | 78 | 10.3 | 42.3 | 1.00 (0.54 to 1.85) | 1.00 | 1.23 (0.64 to 2.34) | 0.53 |
| ≥140/90 | → | ≥140/90 | 29 | 149 | 17.5 | 55.0 | 1.16 (0.71 to 1.90) | 0.55 | 1.29 (0.74 to 2.26) | 0.37 |

BP indicates blood pressure; HR, hazard ratio.

*Data were adjusted for potential confounding covariates in late life, namely, age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

Honolulu-Asia Aging Study revealed that the risks for both AD and VaD increased in Japanese-American men with untreated hypertension in midlife.[24,25] The results of community-based studies conducted in Finland[26] and in China[27] also showed that elevated systolic BP in midlife increased the risk of AD in late life. Conversely, the Hiroshima Study[28] in Japan demonstrated that higher midlife systolic BP was linked to late-life onset of VaD but not to AD. This finding is in accord with ours. The discrepancies in the findings among these studies may be attributable to the difficulty of distinguishing between dementia subtypes. Patients with dementia sometimes have mixed neurodegenerative and vascular pathology.[29] Recently, cognitive impairment in association with vascular factors has received much attention as a treatable condition and has been termed "vascular cognitive impairment," which can occur either alone or in association with AD.[11] Careful ascertainment of the dementia type, using clinical information, neuroimaging, and brain autopsy, may be necessary to assess the true effects of vascular risk factors on the development of dementia. Therefore, we have ascertained the relationship between BP and each dementia subtype in the sensitivity analysis using only definite cases determined by autopsy. Another possible explanation is that the diverse findings may reflect that controlling for confounding factors such as diabetes mellitus and metabolic disorders was lacking or insufficient in the previous studies.

Most notably, the present study demonstrated that subjects with midlife BP of ≥140/90 mm Hg still had a greater risk of VaD, even if their late-life BP was reduced to <140/90 mm Hg. Elevated BP has been found likely to cause small-vessel disease and white-matter lesions.[30,31] Long exposure to poorly controlled midlife hypertension presumably worsens arteriolosclerotic changes and lipohyalinosis in the deep subcortical white matter circuit, which may be less reversible by BP reduction once these changes are established.[13,32] The present findings, therefore, strongly support that hypertension and relevant cardiovascular morbidity in midlife have a great impact on the etiology of VaD.

The strengths of our study include its longitudinal population-based design, long follow-up, evaluation of midlife BP as well as late-life BP, and the availability of neuropathology and neuroimaging data where needed for the ascertainment of dementia types. On the other hand, several limitations of the present study should be noted. First, the fact that there were only 3 measurements of BP on only one occasion in midlife and on another in late life may have led to some degree of misclassification of BP levels. Such a limitation would weaken the association found in the present study, biasing the results toward the null hypothesis. To obtain a precise estimate of the association, a study in which multiple measurements of BP are taken on separate occasions is needed. Second, we were unable to obtain potential confounding factors, such as depressed mood and apolipoprotein E genotype. The lack of this information would result in a bias toward overdiagnosis of dementia and reduce the accuracy of our findings.

### Perspectives

The present study clearly demonstrated that elevated midlife and late-life BP levels are significant risk factors for the late-life onset of VaD but not for AD in a general Japanese population. Higher midlife BP is especially considered to be strongly associated with greater risks of all-cause dementia and VaD, regardless of BP levels in late life. These findings highlight certain important facts, that BP-related pathophysiological processes of dementia begin many years before any symptoms appear and that a clinical history of hypertension and related comorbid disease at that point is likely to have a great impact on the establishment of the disease. To the extent that the adverse effects of long-standing hypertension on small brain vessels and the subsequent development of dementia are less reversible, optimal management of hypertension as early as possible in the life cycle may be an effective approach to preventing late-life dementia in the general population.

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## Disclosures

None.

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# Apolipoprotein Genotype for Prediction of Alzheimer's Disease in Older Japanese: The Hisayama Study

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**OBJECTIVES:** To estimate the effects of the apolipoprotein E (APOE)-ε4 allele on the development of dementia and to elucidate its usefulness in the risk prediction of dementia in Japanese.

**DESIGN:** Prospective cohort study.

**SETTING:** The Hisayama Study, in Japan.

**PARTICIPANTS:** Five hundred twenty-three participants with deoxyribonucleic acid samples from a population of 1,073 community-dwelling participants without dementia aged 60 to 79.

**MEASUREMENTS:** The risk estimates of the APOE-ε4 allele on the development of all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD).

**RESULTS:** During 17 years of follow-up, 136 participants developed dementia, 81 of whom had AD and 39 VaD. After adjusting for age, sex, education, smoking, alcohol intake, systolic blood pressure, use of antihypertensive agents, glycosylated hemoglobin, serum total cholesterol, body mass index, and regular exercise, the risks of all-cause dementia and AD were significantly higher in APOE-ε4 carriers than in noncarriers, but no such association was observed for VaD (all-cause dementia: hazard ratio (HR) = 1.81, $P = .004$; AD: HR = 3.42, $P < .001$; VaD: HR = 1.08, $P = .86$). The area under the receiver operating characteristic curve was significantly greater when the APOE genotype was incorporated into a model with potential risk factors for AD (0.74 vs 0.68, $P = .02$). Other measures of model discrimination (net reclassification improvement: 0.18, $P = .01$; integrated discrimination improvement: 6.25, $P < .001$) also confirmed this improvement in AD risk assessment.

**CONCLUSION:** The APOE-ε4 allele is a risk factor for AD in the Japanese population. Information on APOE genotype improves AD risk assessment substantially beyond a model based on potential risk factors. **J Am Geriatr Soc 59:1074–1079, 2011.**

**Key words: dementia; Alzheimer's disease; vascular dementia; cohort study; APOE**

Dementia is a major cause of disability and premature death in older adults.[1] Alzheimer's disease (AD) has been found to be the most common form of dementia in population-based prospective studies conducted in Western countries. Conversely, vascular dementia (VaD) has been found to be more prevalent in Japan than in Western countries,[2–7] although in recent years the incidence of AD in Japanese has risen to nearly the same level as in Western studies,[4–7] with the result that the burden of AD has been increasing gradually in Japan.[3]

The apolipoprotein (APOE)-ε4 allele has been identified as a susceptibility genotype for AD,[8] but few cohort studies have examined this possibility in Asians.[9,10] Moreover, only a few studies have assessed whether the APOE-ε4 genotype can improve the accuracy with which AD can be predicted.[11,12] An enhanced risk assessment would be of great clinical value if it could more accurately identify people who are at high risk of AD.

Toward this end, a community-based prospective cohort study for evaluating risk factors for dementia in Japanese was established. One achievement of this study was that it verified the subtypes of dementia using a detailed neurological and morphological examination, including neuroimaging and autopsy.[4,13] The purposes of this study were to elucidate the association between the APOE-ε4 allele and the development of dementia and its subtypes, and to investigate the effect of the APOE genotype on the accuracy of AD prediction in Japanese.

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## METHODS

### Study Population

A population-based prospective study of cerebrocardiovascular diseases was established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area of Kyushu Island, Japan. Full community surveys of the health status and neurological condition of residents aged 40 and older have been repeated since 1961.[14] Additionally, comprehensive surveys of cognitive impairment in older adults have been conducted every 6 or 7 years since 1985, and collection of genomic deoxyribonucleic acid (DNA) was started in 2000.

In 1988, 1,073 residents aged 60 to 79 (89.6% of the total population in this age group) participated in a health examination; 534 individuals for whom DNA samples were not available (416 died before the collection of DNA samples was begun, and 118 did not consent to the genomic study) were excluded from the study. The characteristics of the excluded participants are shown in Table 1. Additionally, after excluding 13 individuals with dementia at baseline, two of whom died before starting the follow-up, and one for whom we failed to identify the APOE genotype, the remaining 523 participants (205 men and 318 women) were enrolled in this study.

### Follow-Up Survey

The participants were followed prospectively for 17 years, from December 1988 to November 2005. Detailed information about the follow-up survey on dementia has been described elsewhere.[3,4,13] Briefly, a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office was established. Regular health examinations were given annually to obtain information on any stroke or dementia that the monitoring network missed. Health status was also checked yearly by mail or telephone for any participant who did not undergo regular examinations or who had moved out of town. Follow-up screening surveys of cognitive function were conducted in 1992, 1998, and 2005.[3,4] When new neurological symptoms, including cognitive impairment, were suspected, the study physician and psychiatrist carefully evaluated the participant, conducting comprehensive investigations including interviews of the family or attending physician, physical and neurological examinations, and a review of the clinical records.

### Diagnosis of Dementia

The diagnosis of dementia was made based on the guidelines of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*.[15] Participants diagnosed with AD met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria,[16] and participants diagnosed with VaD met the National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en

**Table 1. Baseline Characteristics of Study Subjects**

| Characteristic | Subjects Included in the Study | | | Subjects for Whom DNA Samples Were Unavailable (n = 534) |
|---|---|---|---|---|
| | Overall (n = 523) | APOE-ε4 Allele | | |
| | | Noncarrier (n = 415) | Carrier (n = 108) | |
| Age, mean ± SD | 66.8 ± 4.9 | 67.1 ± 5.0 | 66.1 ± 4.3 | 70.4 ± 5.6## |
| Male, n (%) | 205 (39.2) | 149 (35.9) | 56 (51.9)** | 289 (45.9)# |
| Education ≤6 years, n (%) | 48 (9.2) | 42 (10.1)* | 6 (5.6) | 72 (13.5)# |
| Systolic blood pressure, mmHg, mean ± SD | 135.3 ± 20.2 | 135.3 ± 20.0 | 135.4 ± 20.9 | 142.6 ± 24.4## |
| Use of antihypertensive agents, n (%) | 116 (22.2) | 93 (22.4) | 23(21.3) | 149 (27.9)# |
| Glycosylated hemoglobin, %, mean ± SD | 5.6 ± 0.7 | 5.7 ± 0.7 | 5.6 ± 0.8 | 5.7 ± 0.8 |
| Serum total cholesterol, mg/dL, mean ± SD | 212.7 ± 40.9 | 212.1 ± 39.5 | 215.1 ± 46.2 | 204.6 ± 46.2## |
| Body mass index, kg/m$^2$, mean ± SD | 22.8 ± 3.0 | 22.7 ± 3.0 | 22.9 ± 3.2 | 22.0 ± 3.2## |
| Smoker, n (%) | 101 (19.3) | 72 (17.3) | 29 (26.9)* | 150 (28.1)## |
| Alcohol drinker, n (%) | 131 (25.0) | 94 (22.7) | 37 (34.3)* | 142 (26.6) |
| Regular exercise (≥3 times/wk), n (%) | 81 (15.5) | 63 (15.2) | 18 (16.7) | 71 (13.3) |
| Duration of follow-up, mean ± SD | 16.0 ± 2.4 | 16.1 ± 2.2 | 15.6 ± 3.0 | 9.7 ± 4.8## |
| Died during follow-up, n (%) | 68 (13.0) | 57 (13.7) | 11 (10.2) | 416 (77.9)## |
| Developed all-cause dementia, n (%) | 136 (26.0) | 102 (24.6) | 34 (31.5) | 154 (28.8) |
| Age at onset of all-cause dementia, mean ± SD | 82.9 ± 5.9 | 83.5 ± 6.0 | 81.2 ± 5.4 | 80.9 ± 5.9## |
| Developed Alzheimer's disease, n (%) | 81 (15.5) | 52 (12.5) | 29 (26.9)** | 67 (12.6) |
| Age at onset of Alzheimer's disease, mean ± SD | 83.0 ± 5.7 | 83.8 ± 5.7 | 81.6 ± 5.5 | 82.0 ± 5.5 |
| Developed vascular dementia, n (%) | 39 (7.5) | 31 (7.5) | 8 (7.4) | 61 (11.4)# |
| Age at onset of vascular dementia, mean ± SD | 82.4 ± 6.1 | 83.2 ± 6.3 | 79.3 ± 4.1 | 80.2 ± 5.8 |

Differences were estimated using the Student *t*-test or the chi-square test as appropriate.

$P<$*.05, **.01: ε4 allele (+) vs ε4 allele (−).

$P<$#.05, ##.01: subjects for whom deoxyribonucleic acid (DNA) samples were not available vs subjects included in the study.

APO = apolipoprotein; SD = standard deviation.

Neurosciences criteria.[17] Possible or probable dementia subtypes were diagnosed according to clinical information, including neuroimaging. Definite dementia subtypes were also determined on the basis of clinical and neuropathological information in participants with dementia who underwent autopsy. The diagnostic procedure for autopsy cases was reported previously.[18] Expert neurologists and psychiatrists adjudicated every dementia case.

During the 17-year follow-up period, 136 participants (45 men and 91 women) developed dementia, and 68 of these died. The mean age of onset of dementia was 83 ± 6 years. Of those who developed dementia, 116 (85.3%) underwent evaluation with neuroimaging, and 61 (44.9%) were subjected to brain autopsy examination. Fifty-seven of the 136 participants were evaluated with both examinations, resulting in 120 participants (88.2%) having a morphological examination. Of the participants with dementia, eight had mixed AD and VaD and were counted as cases in both dementia subtypes. Finally, 81 participants had AD and 39 VaD.

### Single Nucleotide Polymorphism Selection and APOE Genotyping

Genomic DNA was extracted from peripheral blood leukocytes or autopsy tissues using a standard method. Two single nucleotide polymorphisms (SNPs; rs429358 and rs7412) were genotyped using the multiplex polymerase chain reaction–based Invader assay (Third Wave Technologies, Madison, WI)[19] in a blinded fashion to the clinical information of study samples. The accuracy of genotype identification was tested in 94 samples by direct sequencing using the ABI3730 Genetic Analyzer (Applied Biosystems, Foster City, CA), and the concordance rate was 100%. The APOE genotypes were classified into ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4 based on the haplotypes of rs429358 and rs7412. The frequencies of the APOE genotypes in the whole sample were as follows: ε2/ε2, three (0.6%); ε2/ε3, 45 (8.6%); ε3/ε3, 367 (70.2%); ε2/ε4, four (0.8%); ε3/ε4, 94 (18.0%); and ε4/ε4, 10 (1.9%). These genotyped data were strictly controlled under condition of anonymity so that individuals could not be identified.

### Risk Factors

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, antihypertensive treatment, educational status, alcohol consumption, smoking habit, and physical activity. Alcohol consumption and smoking habit were classified as current use or not. Participants engaging in sports at least three times per week during their leisure time were classified as physically active. Sitting blood pressure was measured using a sphygmomanometer three times at the right upper arm after at least 5 minutes of rest, and the mean of the three measurements was used in the analysis. Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m$^2$) was calculated. Glycosylated hemoglobin (HbA1c) was measured using high-performance liquid chromatography (HLC-723Hb, TOSOH, Tokyo, Japan). Plasma total cholesterol levels were measured enzymatically.

### Statistical Analysis

The Cox proportional hazards model was used to estimate the multivariable-adjusted probabilities of event-free survival and the multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of dementia in relation to the APOE genotype. The assumption of the proportional hazards was checked graphically using the log cumulative hazard plots for each dementia subtype according to APOE genotype. The heterogeneity in the relationship between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model.

To compare the accuracy of risk assessment for AD development between the models adjusted for potential risk factors with and without the APOE genotype, receiver operating characteristic (ROC) curves for the model were plotted. The consistency in the area under the ROC curve (AUC) between models was estimated using DeLong's method.[20] The greater discriminative value of the APOE genotype was further examined using two measures previously described:[21] net reclassification improvement and integrated discrimination improvement. In this analysis, the probability of the risk of AD over 17 years was classified into clinically meaningful categories of less than 10%, 10% to 20%, and more than 20%. The individual probabilities were estimated using the Cox proportional hazards model. SAS (version 9.2, SAS Institute, Inc., Cary, NC) and STATA (version 9.2, Stata Corp., College Station, TX) were used to perform statistical analysis. Two-sided $P < .05$ was considered statistically significant in all analyses.

### Ethical Considerations

This study was conducted with the approval of the ethics committees of the Kyushu University Faculty of Medicine and of the RIKEN Yokohama Institute. Written informed consent was obtained from all participants.

## RESULTS

The baseline characteristics of participants are summarized in Table 1 according to the presence or absence of the APOE-ε4 allele. Mean age did not differ between APOE-ε4 carriers and noncarriers, but the proportion of men was higher among APOE-ε4 carriers. The frequencies of smoking and alcohol intake were higher and the frequency of low educational status (≤6 years) was lower in APOE-ε4 carriers than in noncarriers.

As shown in Table 2, APOE-ε4 carriers had significantly higher incidence rates of all-cause dementia (33.0% vs 20.8%, $P = .008$) and AD (28.8% vs 10.2%, $P < .001$) over the 17-year follow-up than noncarriers after adjusting for age, sex, education, smoking, and alcohol intake; no significant differences were observed for VaD. Participants who were APOE-ε4 carriers had significantly greater risk of all-cause dementia (HR = 1.72, 95% CI = 1.15–2.56) than those who were APOE-ε4 noncarriers, after adjusting for the aforementioned risk factors. This association remained significant even in the fully adjusted model including age, sex, education, smoking, alcohol intake, systolic blood pressure, use of antihypertensive agents, HbA1c, serum total cholesterol, BMI, and regular exercise (HR = 1.81, 95% CI = 1.21–2.72). With regard to subtypes of dementia, APOE-ε4 carriers had a 3.4 times (95% CI = 2.12–5.51)

**Table 2. Association Between the Apolipoprotein (APOE)-ε4 Allele and Development of Dementia**

| APOE-ε4 Allele Genotype | Events, n | Participants, n | Adjusted Incidence for 17 Years (%)* | Hazard Ratio (95% Confidence Interval) *P*-Value | | |
|---|---|---|---|---|---|---|
| | | | | Crude | Model 1* | Model 2† |
| All-cause dementia | | | | | | |
| Negative | 102 | 415 | 20.8 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Positive | 34 | 108 | 33.0 | 1.35 (0.92–1.99) .13 | 1.72 (1.15–2.56) <.001 | 1.81 (1.21–2.72) .004 |
| AD | | | | | | |
| Negative | 52 | 415 | 10.2 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Positive | 29 | 108 | 28.8 | 2.28 (1.45–3.59) <.001 | 3.15 (1.97–5.02) <.001 | 3.42 (2.12–5.51) <.001 |
| VaD | | | | | | |
| Negative | 31 | 415 | 6.5 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Positive | 8 | 108 | 7.7 | 1.04 (0.48–2.27) .91 | 1.19 (0.54–2.64) .66 | 1.08 (0.48–2.43) .85 |

For the analysis of incidence of Alzheimer's disease (AD), vascular disease (VaD) cases were censored and vice versa.
*Risk estimates were adjusted for age, sex, education, smoking, and alcohol intake.
†Risk estimates were adjusted for confounding factors included in Model 1 plus systolic blood pressure, use of antihypertensive medication, glycosylated hemoglobin, serum total cholesterol, body mass index, and regular exercise.

greater risk of AD than APOE-ε4 noncarriers in the fully adjusted model, but no such association was observed for VaD. Competing risk models were also run using VaD as a competing risk in the AD model and vice versa. The results remained; in the fully adjusted competing risk model, APOE-ε4 carriers had a greater risk of AD (HR = 2.76, 95% CI = 1.98–3.73) and VaD (HR = 1.09, 95% CI = 0.62–1.91) than noncarriers.

Additionally, the relationship between the number of APOE-ε4 alleles and the risk of AD was elucidated. The fully adjusted HR of AD increased linearly with increasing number of APOE-ε4 alleles (HR = 3.04, 95% CI = 1.84–5.04 for one APOE-ε4 allele; HR = 9.76, 95% CI = 3.62–26.29 for two APOE-ε4 alleles; *P* for trend <.001).

To evaluate the influence of APOE genotype on the accuracy of AD risk assessment, the AUCs of models with and without the APOE genotype were compared. The AUC was significantly greater after adding information on the APOE genotype to the model, including other potential risk factors, namely, age, sex, education, smoking, alcohol intake, systolic blood pressure, use of antihypertensive agents, HbA1c, serum total cholesterol, BMI, and regular exercise (from 0.68, 95% CI = 0.62–0.75 to 0.74, 95% CI = 0.69–0.80; *P* for difference in the area = .02). Reclassifications for participants who did or did not develop AD are summarized in Table 3. When the model with the APOE genotype was used, 15 participants were correctly reclassified into a higher risk category, and 14 were inappropriately reclassified into a lower risk category of participants who developed AD. Alternatively, 137 participants were correctly reclassified into a lower risk category, and 62 were inappropriately reclassified into a higher risk category of participants who did not develop AD. After the addition of the APOE genotype, the net reclassification improvement was estimated as 0.18 ($Z_{NRI} = 2.47$, $P = .01$), and the integrated discrimination improvement was estimated as 6.25 ($Z_{IDI} = 3.75$, $P < .001$).

## DISCUSSION

This long-term prospective study of a general Japanese population demonstrated that APOE-ε4 carriers had a greater risk of developing AD, but not VaD, than noncarriers. This association remained unchanged even after controlling for confounding factors including age, sex, education, smoking, alcohol intake, systolic blood pressure, use of antihypertensive agents, HbA1c, serum total cholesterol, BMI, and regular exercise. To the knowledge of the authors, this is the first prospective study showing that the incorporation of the APOE genotype into a model with

**Table 3. Reclassification of the 17-Year Predicted Absolute Risk of the Development of Alzheimer's Disease (AD)**

| Model 1 | Model 1+APOE Genotype | | | |
|---|---|---|---|---|
| | Participants, n | | | |
| | <10% risk | 10–20% risk | >20% risk | Total |
| Participants who developed AD | | | | |
| <10% risk | 5 | 3* | 2* | 10 |
| 10–20% risk | 12† | 9 | 10* | 31 |
| >20% risk | 0† | 2† | 38 | 40 |
| Total | 17 | 14 | 50 | 81 |
| Participants who did not develop AD | | | | |
| <10% risk | 103 | 28* | 1* | 132 |
| 10–20% risk | 128† | 67 | 33* | 228 |
| >20% risk | 0† | 9† | 73 | 82 |
| Total | 231 | 104 | 107 | 442 |

Model 1 includes age, sex, education, smoking, alcohol intake, systolic blood pressure, use of antihypertensive medication, glycosylated hemoglobin, serum total cholesterol, body mass index, and regular exercise.
Participants were categorized according to the 17-year predicted absolute risks of the development of AD, which were estimated by using the relevant Cox model.
Participants reclassified into
*higher- and
†lower-risk categories after including the apolipoprotein E (APOE) genotype in the model.
Net reclassification improvement was estimated as 0.18 ($Z_{NRI} = 2.47$, $P = .01$).

potential risk factors improved the ability to predict AD in a general population. These findings may provide a useful guide to estimate the risk of AD for the general population.

The APOE-ε4 allele has been found to be an important genetic risk factor for AD in a large majority of epidemiological studies,[8] but few population-based prospective studies have provided evidence for the association between the APOE-ε4 allele and the incidence of AD for Asians.[9,10] The Honolulu-Asia Aging Study[9] of Japanese-American men has evaluated the association between the APOE-ε4 allele and the risk of developing AD and VaD. The results showed that APOE-ε4 carriers had a significant 2.4 times greater risk of AD than noncarriers, but no such association was observed for VaD. The Kame Project,[10] a prospective study of Japanese Americans living in King County, Washington, in the United States, also reported that the APOE-ε4 allele was a strong risk factor for AD. These findings are in accordance with those of the current study.

In the present study, adding the APOE genotype to potential risk factors significantly increased the AUC, although the influence of APOE genotype on the validity of AD risk assessment is inconsistent in previous studies.[11,12] In a hospital-based cross-sectional study, adding the APOE genotype to the clinical information significantly increased the AUC for discriminating true cases of AD.[11] Conversely, the Honolulu-Asia Aging Study[12] showed no significant differences in the AUC for detecting AD between models with and without the APOE genotype. It has been acknowledged that the AUC analysis is insensitive to change in the prediction ability even when a new marker is statistically significant and independently associated with risk.[22] Thus, the current study also evaluated new measures of model discrimination, namely net reclassification improvement and integrated discrimination improvement statistics, which appeared to be more sensitive to change in the prediction ability of the outcomes between risk assessment models than the AUC analysis.[21] The estimates of these statistics showed that the addition of the APOE genotype to the model with potential risk factors improved the discriminatory property of the model for AD prediction in participants without dementia at baseline. These findings suggest that APOE genotype is an important risk factor for predicting accurately the occurrence of AD over time.

APOE is the most common susceptibility gene for AD, but the mechanism underlying its action in the development of AD is not completely understood. A widely accepted hypothesis is that β-amyloid accumulates in the brain, aggregating to form oligomers, plaques, and cerebrovascular deposits.[23] The APOE-ε4 allele is implicated in disordered trafficking of β-amyloid peptide[24] and stimulates its deposition.[25] A postmortem neuropathological study demonstrated that people with AD with the APOE-ε4 allele had stronger amyloid deposition than those without it.[26] These findings indicate that the APOE-ε4 allele may lead to poorer clearance of β-amyloid, causing AD.

The strengths of the current study include its longitudinal population-based study design, long duration of follow-up, and accuracy in the diagnosis of dementia, including its subtypes. Some limitations should be noted. First, there was selection bias in the study population. Individuals excluded from the study had more cardiovascular risk factors, greater mortality, and higher cumulative incidence of VaD than those included in the study at baseline (Table 1), but there was no significant difference in the cumulative incidence of AD between participants excluded and included. Thus, the generalizability of the findings in regard to VaD may be limited. Nevertheless, the present findings provide useful information for assessing the risk of AD. Second, despite the use of detailed findings from autopsy, brain imaging, and clinical information, a certain degree of subtype misclassification cannot be excluded because the boundary between VaD and AD is not always discernible, and participants with dementia sometimes have mixed neurodegenerative and vascular pathology.[27] However, a sensitivity analysis using only events determined to be pure cases of AD and VaD did not make any material difference in the findings (data not shown).

In conclusion, the APOE-ε4 allele is an independent risk factor for the development of AD in a general Japanese population. Moreover, the fact that adding the APOE genotype to the model significantly improved its ability to predict the risk of AD suggests that the APOE-ε4 allele should be considered an essential risk factor for predicting AD. Further investigations are required to establish a more-reliable risk assessment for AD.

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**Conflict of Interest:** The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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# Association of Alzheimer disease pathology with abnormal lipid metabolism

## The Hisayama Study

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ABSTRACT

**Objective:** The relationship between lipid profiles and Alzheimer disease (AD) pathology at the population level is unclear. We searched for evidence of AD-related pathologic risk of abnormal lipid metabolism.

**Methods:** This study included brain specimens from a series of 147 autopsies performed between 1998 and 2003 of residents in Hisayama town, Japan (76 men and 71 women), who underwent clinical examinations in 1988. Lipid profiles, such as total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDLC), were measured in 1988. Low-density lipoprotein cholesterol (LDLC) was calculated using the Friedewald formula. Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines (CERAD) and neurofibrillary tangles (NFTs) were assessed according to Braak stage. Associations between each lipid profile and AD pathology were examined by analysis of covariance and logistic regression analyses.

**Results:** Adjusted means of TC, LDLC, TC/HDLC, LDLC/HDLC, and non-HDLC (defined as TC-HDLC) were significantly higher in subjects with NPs, even in sparse to moderate stages (CERAD = 1 or 2), compared to subjects without NPs in multivariate models including *APOE* $\epsilon$4 carrier and other confounding factors. The subjects in the highest quartiles of these lipid profiles had significantly higher risks of NPs compared to subjects in the lower respective quartiles, which may suggest a threshold effect. Conversely, there was no relationship between any lipid profile and NFTs.

**Conclusion:** The results of this study suggest that dyslipidemia increases the risk of plaque-type pathology. *Neurology*® 2011;77:1068-1075

GLOSSARY

**AD** = Alzheimer disease; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **HDLC** = high-density lipoprotein cholesterol; **LDLC** = low-density lipoprotein cholesterol; **NFT** = neurofibrillary tangle; **NP** = neuritic plaque; **OR** = odds ratio; **TC** = total cholesterol; **TG** = triglycerides.

To elucidate the association of lifestyle diseases with Alzheimer disease (AD) pathology, a large-scale, population-based clinicopathologic study is required. Since 1961, we have been conducting a long-term prospective cohort study of cerebro-cardiovascular diseases in the town of Hisayama, a suburb of Fukuoka City in Japan. Careful surveillance of cognitive impairment was started from 1985, which was carried out through a daily monitoring system established by the study team, local practitioners, and the town government. In a series of studies, we have reported the incidence and survival of dementia,[1] and trends in the prevalence of AD and vascular dementia.[2] These studies indicate that the prevalence of AD is increasing at an accelerating pace in parallel with an increase of metabolic disorders. Recently, we also reported that insulin

Supplemental data at www.neurology.org

Supplemental Data

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