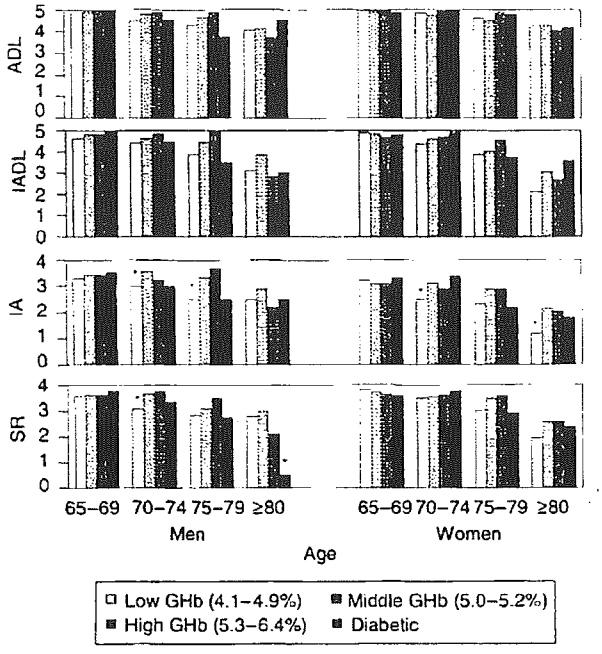

Figure 1. Relationship between activity scores and glycated hemoglobin (GHb) group, classified by sex and age. *Significant difference ($P<.05$) compared with middle GHb (5.0–5.2%) group of the same sex and age stratum. ADL = activity of daily living; IADL = instrumental activity of daily living; IA = intellectual activity; SR = social role.

GHb, and diabetic groups were compared with the middle GHb group as a reference. In four of the eight strata (men aged 70–74, men aged 75–79, women aged 70–74, and women aged ≥80), the low GHb group had significantly lower IA than the middle GHb group ($P<.05$). In one stratum (men aged 70–74), those with low GHb had significantly lower SR than those with middle GHb ($P<.05$); in another stratum (men aged ≥80), the diabetic group had lower SR than the middle GHb group ($P<.05$). Thus, subjects aged 70 and older with low GHb appeared to have low IA for their age.

A multiple linear regression model for subjects younger than 70 (Table 2) showed that lower IA score was significantly and independently associated with female sex, history of stroke, visual impairment, lowest education class, and physical occupation class ($P<.05$). GHb levels were not associated with IA in this model or in another model using logistic regression.

A corresponding analysis for the subjects aged 70 and older (Table 2) showed that lower IA was associated with the factors above, plus higher age, intermediate education class, intermediate occupation class, low GHb group, and lower albumin ($P<.05$). In this model, IA score for the low GHb group was estimated at 0.51 points lower than the middle GHb group—an average after multivariate adjustment. This effect size is equivalent to 8.9 years of aging, because IA decreased with age by 0.57 points per 10 years. An alternative analysis using a multiple logistic regression model yielded a similar result, with the disadvantageous effect of a low GHb being statistically significant in those aged 70 and older ($P<.001$).

To avoid confounding, further regression analyses were performed in a selected subgroup of the subjects aged 70 and older (those with stroke history or impaired IADL were excluded), introducing depressive mood and BMI as additional explanatory variables. In a linear regression (Table 2), the low GHb group still showed a significantly lower IA score than the middle GHb group, by 0.45 points after multivariate adjustment ($P<.001$). The high GHb also showed lower IA, by 0.24 points, which was statistically significant ($P=.04$). The diabetic group was not significantly different from the middle GHb group in IA, although the point estimate suggested that it had lower IA. Thus, the relationship between GHb and IA was of an inverted U-shape in nondiabetic subjects. Femle sex visual impairment, low education, and intermediate occupation remained significant factors ($P<.05$), whereas age, intermediate education, and physical occupation dropped out. The effect of albumin was reduced and dropped out as a statistically significant associating factor; this change from the former analysis was not attributable to the inclusion of BMI as an additional explanatory variable. An alternative analysis, using multiple logistic regression, indicated statistically significant inverse associations between IA and low GHb ($P<.001$) and high GHb ($P=.03$).

A multiple logistic regression using a square term with GHb as a continuous variable showed borderline significance of the square term ($P=.06$) in these nondiabetic, stroke-free, and IADL-intact subjects aged 70 and older. The GHb value corresponding to the optimal IA was estimated at 5.2%.

DISCUSSION

The present study examined the association between GHb and aspects of daily activities in an elderly population, and found an age-specific association between GHb and IA. In nondiabetic subjects aged 70 and older and without history of stroke or IADL impairments, an inverted U-shaped association was observed between GHb and IA, independent of other risk factors. The value of GHb related to the maximum IA score was 5.0% to 5.2%, on the basis of comparison of tertiles; or 5.2%, assuming a logistic regression model including a squared term with GHb as a continuous variable. A similar relationship was observed also in the whole sample aged 70 and older but not in the younger counterpart.

Although this cross-sectional study cannot specify any causality, an extrapolation from results of experimental studies provides a possible explanation for the low IA with low GHb. Previous studies have shown that glucose ingestion can enhance memory.[1–10,24] The precise mechanism has not been established, but an animal study reported that a demanding memory task induced a decrease in hippocampal extracellular glucose concentration and that a systemic administration of glucose prevented such a decrease while enhancing memory task performance.[25] If the mechanism of memory enhancement via glucose is dependent on blood glucose concentration per se, such as what is expected for facilitated diffusion, an effect of acutely raised glucose concentration should be replicated as a consequence of a

Table 2. Relationship Between Intellectual Activity Score* and Selected Subgroup Characteristics in Multiple Linear Regression Models

Characteristic	Aged <70 (n = 361)			Aged ≥70 (n = 568)			Aged ≥70, Intact Instrumental Activities of Daily Living, and No Stroke History (n = 353)		
	Regression Coefficient	(95% Confidence Interval)	*P*-value	Regression Coefficient	(95% Confidence Interval)	*P*-value	Regression Coefficient	(95% Confidence Interval)	*P*-value
Female†	−0.32	(−0.54 to −0.11)	.003	−0.46	(−0.66 to −0.26)	<.001	−0.21	(−0.41 to −0.01)	.04
Age (per 10 years)	−0.02	(−0.72–0.67)	.95	−0.57	(−0.76 to −0.38)	<.001	−0.10	(−0.32–0.13)	.41
History of stroke†	−0.75	(−1.18 to −0.33)	<.001	−0.88	(−1.21 to −0.55)	<.001			
Visual impairment†	−0.56	(−1.07 to −0.05)	.03	−0.76	(−1.08 to −0.44)	<.001	−0.56	(−0.94 to −0.19)	.004
Auditory impairment†	0.12	(−0.30–0.54)	.57	−0.06	(−0.30–0.19)	.65	0.03	(−0.26–0.31)	.84
Depressive mood (15-item Geriatric Depression Scale score ≥6)†							−0.18	(−0.40–0.03)	.10
Educational class									
High		Reference			Reference			Reference	
Intermediate†	−0.21	(−0.55–0.12)	.22	−0.39	(−0.72 to −0.06)	.02	−0.22	(−0.51–0.07)	.15
Low†	−1.49	(−2.14 to −0.83)	<.001	−1.26	(−1.77 to −0.76)	<.001	−1.33	(−1.84 to −0.81)	<.001
Past occupational class									
Intellectual		Reference			Reference			Reference	
Intermediate†	−0.08	(−0.40–0.25)	.65	−0.67	(−1.01 to −0.32)	<.001	−0.49	(−0.81 to −0.18)	.003
Physical†	−0.43	(−0.80 to −0.07)	.02	−0.48	(−0.88 to −0.07)	.02	−0.34	(−0.72–0.04)	.08
Glycated hemoglobin group									
Low (4.1–4.9%)†	0.13	(−0.13–0.38)	.34	−0.51	(−0.74 to −0.27)	<.001	−0.45	(−0.69 to −0.21)	<.001
Middle (5.0–5.2%)		Reference			Reference			Reference	
High (5.3–6.4%)†	0.13	(−0.13–0.39)	.33	−0.20	(−0.43–0.04)	.10	−0.24	(−0.46 to −0.02)	.04
Diabetic†	0.24	(−0.14–0.62)	.22	−0.28	(−0.64–0.07)	.11	−0.14	(−0.51–0.24)	.47
Albumin (per 10 g/L)	0.31	(−0.14–0.75)	.18	0.69	(0.31–1.07)	<.001	−0.25	(−0.69–0.19)	.27
Body mass index (kg/m^2)							0.01	(−0.01–0.04)	.35

* Range 0 (worst) to 4 (best).
† Effect of presence compared with absence.
‡ Effect of the category compared with the reference category.

chronically higher level of blood glucose. Thus, individuals with higher GHb within a specific range would do better in performing specific activities that demand memory. Intuitively, it seems reasonable to assume that IA items reflect cognitive functions, including memory, in addition to visual function, mood, education, social circumstances, and so on, considering the generally large prevalence of dementia and memory impairment in the population of this age. Empirical supports are not available now, but the Functional Activities Questionnaire,[26] which assesses 10 items similar to those of IADLs and IA, has been shown to discriminate mildly demented patients from normal adults even better than the Lawton IADL scale.[11,27] On the assumption above, a possible interpretation of the observed association would be that inadequate blood glucose concentrations contribute to low IA scores in the low GHb group.

An alternative explanation that needs to be examined is that cognitive impairment or an intellectually inactive lifestyle may have reduced food consumption and thus blood glucose. Malnutrition from functional decline may indeed have contributed to the positive correlation between albumin level and IA in those aged 70 and older, but after controlling for albumin concentrations, the low GHb subjects still had lower IA scores than the middle GHb group. Furthermore, the association with low GHb concentrations was evident even in the selected subset of healthy elderly, in whom albumin concentrations no longer showed any association with IA. Thus, malnutrition sufficient to decrease serum albumin cannot account for the link between low GHb and low IA score.

Another alternative addresses qualitative differences in diet according to social class. If individuals in low social classes are intellectually inactive and if they eat a diet that does not raise blood glucose, this may lead to an association between low GHb and low IA. In accordance with this notion, the low GHb group included fewer highly educated individuals than the middle GHb group. Nevertheless, the notion would not effectively account for the association between low GHb and low IA that was observed after controlling for educational and occupational classes. Furthermore, it could not explain why the association between low GHb and low IA is restricted to persons aged 70 and older.

If depression was associated with IA and blood glucose, mood state might also be a potential confounder. An earlier cross-sectional study[28] indicated an inverse association between insulin resistance and depression, although depressive mood was not significantly associated with low GHb in the present data. Furthermore, multivariate analysis demonstrated an association between low GHb and low IA independent of mood. Thus, a common relationship with mood state cannot explain the association.

The inclusion of individuals with clinical or subclinical neurodegeneration might be relevant to the observed association. One retrospective study[29] based on autopsy and medical records indicated that patients with Alzheimer's disease (AD) had low GHb levels 6 to 12 months before death. Low GHb is not a consistent finding in AD,[10] but if this were the case, the inclusion of AD patients could give rise to an association between low GHb and low IA score. From this viewpoint, it is important that the association between low GHb and IA was demonstrated even in the subgroup with intact IADLs. This implies that, if low GHb accompanies neurodegenerative processes leading toward AD, it emerges before overt manifestation of dementia and may therefore play a role in progression of the disease.

Limitation of the association between low GHb and low IA to those aged 70 and older is analogous to the preferential benefit from the acute administration of glucose in older subjects.[7] Such selectivity could reflect a ceiling effect in IA measurements in younger subjects or an age-related difference in the susceptibility of IA to changes in glucose. Explanations for the latter could include age-related decreases in cerebral blood flow and in the efficiency of glucose transfer across the blood–brain barrier. Cerebral cortical blood flow decreases with age,[30] and decreases in glucose transporters have been noted in the brain microvessels, the cerebral neocortex, and the hippocampus of patients with AD.[31]

Although GHb provides a reliable index of integrated blood glucose levels over the preceding 2 to 3 months, it does not reflect occasional or diurnal variations.[32,33] Future studies should thus examine whether individuals with low GHb experience hypoglycemia occasionally or nocturnally. In addition, hormonal disturbances may accompany low GHb, particularly changes in insulin level, which can modulate memory.[34,35] The possible relevance of hormonal factors is another matter for future studies.

The present study lacked performance-based assessments of cognitive function, so it is unclear whether cognitive function links GHb and IA, although intellectual activity per se is an important aspect of daily life, with relevance to the quality of life. It also predicts whether IADL will be maintained or will decline in the future.[21] The current findings augment knowledge about the determinants of this informative index.

This study presented a characteristic pattern of association between GHb and IA. Although the causation cannot be determined, the findings appear consistent with the idea that glucose enhances functional performance not only in laboratory tasks but also in daily life. In addition, it suggests that a considerable proportion of older individuals might benefit from glucose administration. Further research seems warranted on the potential of glucose as a cognitive enhancer. Another implication is the need for epidemiological studies of the link between glucose metabolism and cognitive function. Such investigations should take account of a possible nonlinear relationship. Finally, GHb appears to be a useful method of examining the possible disadvantages of low blood glucose levels.

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