

Correlation between cardiovascular risk factors and cognitive decline

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The number of people suffering from dementia in the world is progressively increasing due to the expansion of the geriatric population in which this clinical condition is more frequent. The appearance of a variable degree of cognitive decline up to full-blown dementia does not, however, represent the inevitable fate of those who age, as the studies conducted in the centenarians clearly indicate. Indeed, the age-specific incidence of dementia has progressively decreased in many geographical areas, probably due to an improvement in lifestyles and health care. In fact, a growing number of scientific evidence shows how chronic exposure over the course of life, starting from young adulthood, to various risk factors—arterial hypertension, diabetes mellitus, obesity, tobacco smoke, sleep disorders—contribute significantly to the development of cognitive decline and dementia in the course of senescence. These risk factors, in fact, can trigger and amplify the various neuropathological mechanisms underlying the development of decline, progressively reducing the functional reserve of the brain. Although definitive evidence deriving from *ad hoc* intervention studies is not currently available, it is legitimate to assert that the early control of cardiovascular risk factors can represent today the most effective tool for the prevention of dementia.

Introduction

The number of people suffering from dementia in the world is gradually increasing due to the progressive expansion of the geriatric population in which this clinical condition is more frequent and the enormous spread of cardiovascular risk factors in the general population. The development of a variable degree of cognitive deficit up to overt dementia, both vascular and Alzheimer's type, represents, in fact, a rather common occurrence in those who have been exposed to various cardiovascular risk factors during their life.¹⁻³ The potential of cardiovascular risk factors to contribute to dementia begin to manifest rather early, which is why their prompt correction is essential before they can

trigger and amplify the pathophysiological mechanisms underlying cognitive decline.

Hypertension

The presence of hypertension in young adulthood is associated with an increased risk of dementia in old age.^{3,4} In the Framingham Offspring cohort of 1440 middle-aged individuals (mean 55 years), the presence of systolic blood pressure >140 mmHg was associated over an 18-year follow-up with a 60% increased risk of dementia [hazard ratio 1.6, 95% confidence interval (CI) 1.1-2.4].⁵ The persistence of high blood pressure even in old age (average 60 years) was associated with a further increase in risk (hazard ratio 2.0, 95% CI 1.3-3.1). In contrast, in individuals with optimal control of all cardiovascular risk factors, a significant reduction in the risk of developing both vascular type (hazard

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ratio 0.5, 95% CI 0.3-0.8) or Alzheimer's (hazard ratio 0.8, 95% CI between 0.6 and 1.0) was documented. Similar results were found in an English cohort of 8639 civil servants in which the finding of blood pressure values >130 mmHg at the age of 50, but not at the age of 60 or 70, was associated with an increased risk of dementia (hazard ratio 1.4, 95% CI 1.1-1.8),⁶ further increased risk in subjects with persistent systolic blood pressure >130 mmHg over the age of 45-61 years, even in the absence of cardiovascular disease (hazard ratio 1.3, 95% CI 1.3-1.7).⁶

Numerous observational and intervention studies over the last few years have led to the hypothesis that antihypertensive treatment may represent a valuable tool to prevent the onset of cognitive impairment and dementia.^{3,4} Four recently published meta-analyses have produced unambiguous evidence of a reduction in dementia during antihypertensive treatment without significant differences in terms of protective efficacy between the different classes of drugs. Indeed, the evidence derived from clinical studies is not completely defined mainly due to the short duration of the various therapeutic interventions tested from time to time with respect to the pathophysiological course of the disease and the lack in many of these studies of a clear diagnostic characterization of dementia or mild cognitive impairment (MCI). Quite recently, the results of the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRIN MIND) study have provided new and more vigorous support to the hypothesis of a possible prevention of dementia through an effective treatment of arterial hypertension, producing the first convincing demonstration of the efficacy of antihypertensive therapy in preventing senile cognitive decline.⁷ The study, conducted in hypertensive individuals (mean age 68 years) at increased cardiovascular risk (but with no history of stroke or diabetes), randomized to standard antihypertensive treatment (target systolic blood pressure < 140 mmHg) or intensive (target systolic blood pressure < 120 mmHg) provided the first demonstration of a significant reduction in the risk of developing MCI (14.6 vs. 18.3 cases per 1000 person-years, hazard ratio 0.81, 95% CI 0.69-0.95) in patients assigned to intensive treatment. It is interesting to note that in elderly patients the impact of arterial hypertension on cognitive decline tends to become progressively less evident while the impact of low blood pressure becomes more and more relevant.⁴ The causes of this association between low blood pressure and cognitive decline are probably to be found in the reduction of cerebral blood flow due to the low pressure in a vascular bed which, due to age and/or chronic exposure to cardiovascular risk factors, has lost much of its self-regulating ability.⁴ Therefore, the evidence of a more rapid cognitive decline in elderly patients with low blood pressure induced by antihypertensive treatment, but not in those spontaneously hypotensive, is not surprising.⁴ It is therefore evident the importance of avoiding excessive low blood pressure values in the elderly, and of routinely seeking orthostatic hypotension as this condition, very often iatrogenic, is associated with an increased risk of cognitive decline and dementia.⁴ The development of dementia, however, is often associated with a decrease in blood pressure, probably determined, at least in part, by the development of a variable

degree of cerebral atrophy connected to the pathogenesis of dementia.

Diabetes

Type 2 diabetes mellitus is associated with a significant increased risk of dementia.³ A recent meta-analysis of 14 cohort studies involving a total of 2.3 million individuals with type 2 diabetes mellitus, including 102 174 also suffering from dementia, demonstrated a significant increased risk of dementia (relative risk 1.6, 95% CI 1.5-1.8 for women and 1.6, 95% CI 1.4-1.8 for men) with a direct relationship between disease duration and severity and risk of developing dementia.⁸ These epidemiological evidences offer the pathophysiological equivalent of the sharing between the two morbid entities of important pathophysiological determinants, such as the condition of insulin resistance, increased oxidative stress, and chronic micro-inflammation, so much so as to encourage researchers to label Alzheimer's disease as 'type 3 diabetes mellitus'.⁹ The possibility of a protective effect against cognitive decline by the various anti-diabetes treatments is still to be verified as few studies are concerned with this issue. A meta-analysis of cohort studies conducted in diabetic patients demonstrated a reduced prevalence of cognitive dysfunction in the cross-sectional analysis (3 studies, odds ratio 0.6, 95% CI 0.4-0.8) and a reduced incidence of dementia in the longitudinal analysis (6 studies, odds ratio 0.8, 95% CI 0.4-0.9) in patients taking metformin vs. patients treated with other drugs or not treated.³ These results, certainly encouraging, were not confirmed in a second meta-analysis which did not show any protective effect of metformin (3 studies, relative risk 1.1, 95% CI 0.5-2.4) and a possible adverse effect of insulin treatment (risk relative 1.2, 95% CI 1.1-1.4), the latter result probably unreliable because it is not corrected for the greater severity of the diabetic disease in patients requiring insulin therapy.³ A Cochrane review of clinical trials comparing standard or intensive hypoglycaemic regimens (11 140 patients with a 5-year follow-up) found no influence of intensive treatments on the development of cognitive decline (relative risk 1.0, 95% CI 0.9-1.1) or dementia (relative risk 1.3, 95% CI 1.9-1.9).³

Obesity

The relationship between excess weight and cognitive decline was the subject of a recent review of 19 longitudinal studies, for a total of 589 649 individuals aged 35-65 followed up over period of 42 years.¹⁰ The results demonstrate an increased risk of dementia in patients with overt obesity (body mass index—BMI >30 kg/m², relative risk 1.3, 95% CI 1.1-1.6) but not in overweight subjects (BMI 25-30 kg/m², relative risk 1.1, 95% CI 1.0-1.2).¹⁰ A further meta-analysis, based on the individual data of 1 349 857 adults included in 39 cohort studies, demonstrated a different risk of dementia associated with excess weight in relation to the different duration of the observation period.¹¹ In particular, the risk of dementia associated with each 5 kg/m² increase in BMI was increased when BMI was

assessed more than 20 years prior to the diagnosis of dementia (hazard ratio 1.1.6, 95% CI 0.66-0.77), but not when it was evaluated in shorter time intervals (hazard ratio at 10 years: 0.71, 95% CI 0.66-0.77; hazard ratio between 10 and 20 years: 0.94, 95% CI 0.89-0.99). These results suggest on the one hand that the dementia implications of excess weight is expressed over decades, and on the other, a reverse-causality effect that makes excess weight apparently protective when its relationship with cognitive decline is evaluated in shorter intervals.¹¹ The evidence of a possible protective effect of weight loss in relation to the development of cognitive decline further supports the negative influence of excess weight on cognition.³ A meta-analysis of 7 randomized controlled trials (468 participants) and 13 longitudinal studies (551 participants), which enrolled adult subjects (mean age 50 years) with overweight or overt obesity but without evidence of dementia, demonstrated significant improvement in attention and memory in subjects with BMI >25 following a weight decrease of at least 2 kg occurring in a time interval between 2 and 12 months.³

Cigarette smoke

Smokers are exposed on the one hand to an increased risk of dementia and on the other to an increased probability of dying before the age in which dementia most frequently develops, the latter aspect which inevitably represents an interpretative bias of the relationship between smoking and risk of dementia which in the past has even led to the hypothesis that smoking could represent a protective factor in respect of dementia.³ Indeed, quitting smoking, even in the geriatric age, reduces the risk of dementia. A recently published cohort study, which included 46 140 men aged >60 years, demonstrated a reduced risk of dementia in subjects who had never smoked (hazard ratio 0.81, 95% CI 0.71-0.91) and in those who had stopped smoking for at least 4 years (hazard ratio 0.86, 95% CI 0.75-0.99) compared to those who continued to smoke.¹² Considering the two main types of dementia separately, the risk of Alzheimer's disease was reduced in non-smokers (hazard ratio 0.82, 95% CI 0.70-0.96) compared to smokers while the risk of vascular dementia was reduced in both non-smokers (hazard ratio 0.82, 95% CI 0.70-0.96) compared to smokers (hazard ratio 0.71, 95% CI 0.54-0.95) and in those who had quit for at least 4 years (hazard ratio 0.68, 95% CI 0.48-0.96). The dementia potential of smoking appears troubling in relation to the enormous spread of smoking and the large proportion of individuals exposed to passive smoking, estimated at 35% of non-smoking adults and 40% of children. Exposure to passive smoking, in fact, is associated with a greater deterioration of memory proportional to the duration of exposure.³

Sleep disorders

Over the last few years, scientific literature has shown growing interest in the hypothesis that sleep disorders may affect an increased risk of developing both cardiovascular events and dementia.³ Two recently published meta-

analyses have provided the same demonstration of a significant increase in the risk of dementia in patients with sleep disturbances in general (short or long sleep duration, sleep quality declines, circadian rhythm disturbances, insomnia, obstructive apnoea). These sleep disturbances were associated with an increased risk of dementia in general (hazard ratio 1.2, 95% CI 1.1-1.3) and Alzheimer's disease (hazard ratio 1.6, 95% CI 1.3-1.9).^{12,13} The relationship between sleep duration and risk of cognitive decline appears to have a U trend, with an increased risk of dementia in general and Alzheimer's disease for a sleep duration <5 h (hazard ratio 2.6, 95% CI 1.4-5.1) or >10 h (hazard ratio 2.2, 95% CI 1.4-3.5) compared to a sleep duration between 7 and 10 h.³ These results suggest the opportunity to better correct sleep disorders also with a view at preventing cognitive decline. In this regard, it is important to underline the different potential impact of the various treatments for insomnia on cognitive functions. A recent retrospective cohort study, which analysed data from 268 170 50-year-old subjects, demonstrated an increased risk of Alzheimer's disease in subjects taking benzodiazepines or zolpidem (hazard ratio 1.75, 95% CI 1.67-1.82) compared to subjects who were not taking such drugs.¹⁴ This risk was increased independent of the dose of hypnotic sedatives taken and of the half-life of the benzodiazepines used and was especially evident in case of prolonged exposure (hazard ratio 1.78, 95% CI 1.60-1.99) and use of long half-life benzodiazepines (hazard ratio 1.77, 95% CI 1.65-1.89).¹⁴ In contrast, the use of prolonged-release melatonin was associated with improved cognitive function in patients with early-stage Alzheimer's disease and insomnia, evidence suggesting the use of this drug for the management of sleep disorders in patients with neurocognitive problems.¹⁵

Combined risk factors

The coexistence of multiple cardiovascular risk factors considerably increases the risk of cognitive decline. The Coronary Artery Risk Development in Young Adults (CARDIA) study, for example, demonstrated how cumulative exposure to various cardiovascular risk factors starting from adolescence is associated with worse cognitive performance over a 25-year observation period, with a prevalent impairment of executive functions and verbal memory.⁴ More recently, a study conducted in the UK enrolled 7899 individuals aged 50, followed over a 25-year follow-up, in which a risk score was calculated based on some recognized determinants of behavioural cardiovascular risk (smoking, physical activity, diet, BMI) or biological (blood pressure, cholesterol, and glycaemia), each parameterized on a three-point metric scale.³ The risk of dementia was reduced in individuals with a better score (hazard ratio 0.9, CI 0.9-1.0 for each point of increase in the score), evident both for behavioural factors (hazard ratio 0.9, CI 0.8-0.9 for each point increase of the score) and for the biological parameters (hazard ratio 0.9, CI 0.8-1.0 for each point of increase of the score). The study also demonstrated an association between the risk score, the level of hippocampal atrophy, and brain volume.

Conclusions

The progressive ageing of the population is causing a progressive expansion of those age groups in which the susceptibility to developing dementia is greater. Prevention is today more than ever the only truly successful strategy against dementia. The association between exposure from young adulthood to various cardiovascular risk factors and the subsequent development in old age of a variable degree of cognitive decline up to overt dementia, both vascular and Alzheimer's type, is supported by robust epidemiological and pathophysiological evidence and by some intervention studies.³ This evidence provides the encouraging prospect of being able to stem the spread of dementia through optimal and early control of the main risk factors. Pending the definitive clarification of the pathophysiological mechanisms underlying this evident relationship between cardiovascular risk factors and dementia and that large-scale tools are available for an early diagnosis of an initial cognitive decline, considering the devastating clinical and socio-economic impact of dementia has a profound ethical as well as clinical sense to draw from the numerous scientific evidence already available a further stimulus to seek with determination the optimal control of the global cardiovascular risk in all patients.

Conflict of interest: none declared.

References

- de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* 2014; **12**:130.
- Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer RA, Coker LH, Sidney S. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation* 2014; **129**:1560-1567.
- Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020; **396**:413-446.
- Desideri G, Bocale R. Is there a relationship between blood pressure values and dementia? *Eur Heart J Suppl* 2020; **22**(Suppl L):L61-L65.
- McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, Seshadri S. Blood pressure from mid- to late life and risk of incident dementia. *Neurology* 2017; **89**:2447-2454.
- Abell JG, Kivimäki M, Dugravot A, Tabak AG, Fayosse A, Shipley M, Sabia S, Singh-Manoux A. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. *Eur Heart J* 2018; **39**:3119-3125.
- Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Erus G, Fine LJ, Gaussoin SA, Harris D, Hsieh M-K, Johnson KC, Kimmel PL, Tamura MK, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nasrallah IM, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco MV, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT, Wright CB; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA* 2019; **321**:553-561.
- Chatterjee S, Peters SA, Woodward M, Arango SM, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M, Hassing LB, Hayden KM, Kiyohara Y, Larson EB, Li C-Y, Ninomiya T, Ohara T, Peters R, Russ TC, Seshadri S, Strand BH, Walker R, Xu W, Huxley RR. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2-3 million people comprising more than 100,000 cases of dementia. *Diabetes Care* 2016; **39**:300-307.
- Burillo J, Marqués P, Jiménez B, González-Blanco C, Benito M, Guillén C. Insulin resistance and diabetes mellitus in Alzheimer's disease. *Cells* 2021; **10**:1236.
- Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, Egan K. Body mass index in midlife and dementia: systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. *Alzheimers Dement (Amst)* 2017; **8**:165-178.
- Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, Knutsson A, Koskenvuo M, Kuosma E, Nordin M, Suominen SB, Theorell T, Vuoksima E, Westerholm P, Westerlund H, Zins M, Kivipelto M, Vahtera J, Kaprio J, Singh-Manoux A, Jokela M. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement* 2018; **14**:601-609.
- Shi L, Chen S-J, Ma M-Y, Bao Y-P, Han Y, Wang Y-M, Shi J, Vitiello MV, Lu L. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. *Sleep Med Rev* 2018; **40**:4-16.
- Bubu OM, Brannick M, Mortimer J, Umasabor-Bubu O, Sebastião YV, Wen Y, Schwartz S, Borenstein AR, Wu Y, Morgan D, Anderson WM. Sleep, cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep* 2017; **40**:zsw032.
- Lee J, Jung SJ, Choi JW, Shin A, Lee YJ. Use of sedative-hypnotics and the risk of Alzheimer's dementia: a retrospective cohort study. *PLoS One* 2018; **13**:e0204413.
- Palagini L, Manni R, Aguglia E, Amore M, Brugnoti R, Bioulac S, Bourgin P, Micoulaud Franchi J-A, Girardi P, Grassi L, Lopez R, Mencacci C, Plazzi G, Maruani J, Minervino A, Philip P, Royant Parola S, Poirrot I, Nobili L, Biggio G, Schroder CM, Geoffroy PA. International expert opinions and recommendations on the use of melatonin in the treatment of insomnia and circadian sleep disturbances in adult neuropsychiatric disorders. *Front Psychiatry* 2021; **12**:688890.