Impact of interventions scenarios targeting three main vascular risk factors on the future burden of dementia in France.

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Abstract

The epidemiological and societal burden of dementia is expected to increase in the coming decades due to the world population aging. In this context, the evaluation of the potential impact of intervention scenarios aiming at reducing the prevalence of dementia risk factors is an active area of research. However, such studies must account for the associated changes in mortality and the dependence between the risk factors. Using micro-simulations, this study aims to estimate the changes in dementia burden in France in 2040 according to intervention scenarios targeting the prevention of hypertension, diabetes and physical inactivity. Accounting for their communality and their effects on mortality, the results show that the disappearance of hypertension, diabetes and physical inactivity in France in 2020 could decrease dementia prevalence by 33% among men and 26% among women in 2040 and increase the life expectancy without dementia at age 65 by 3.4 years (men) and 2.6 years (women). Among the three factors, the prevention of hypertension would be the most efficient. These projections rely on current estimates of the risk of dementia and death associated with risk factors. Thanks to the R package developed they could be refined for different countries or different interventions and updated with new estimates.

Introduction

The number of people living with dementia was estimated to be 50 million in 2018 and could increase to 152 million by 2050 due to the population aging [1]. As treatments failed to cure or even slow clinical progression [2], several expert groups recommend focusing on prevention by intervening on modifiable risk factors [3, 4]. Among modifiable risk factors, many studies support a deleterious effect of hypertension [4, 5, 6], diabetes [4, 6, 7, 8] and physical inactivity [4, 6, 9] on the risk of dementia.

Several studies have evaluated the reduction in dementia burden that could be expected by interventions targeting modifiable risk factors. Using the population attributable risk, Barnes and Yaffe [10] estimated that about 50% of AD cases worldwide could be attributed to 7 modifiable risk factors (diabetes, hypertension, obesity, smoking, depression, low educational attainment, and physical inactivity) and they forecasted the number of cases that could be prevented by a reduction in the prevalence of these factors. Accounting for the non-independence of these risk factors, the estimated population attributable risk for the 7 factors combined was reduced to 28% [6]. More recently, the population attributable risk was estimated at 40% for 12 modifiable risk factors accounting for their communality [4]. However, these estimations suffer from an important shortcoming as the population attributable risk does not take into account mortality. As several of these factors have an impact on mortality, their neutralization could extend the life-expectancy and therefore mechanically increase the occurrence of dementia.

Using forward calculation based on multi-state models that distinguish mortality with and without dementia, some authors have assessed the impact on future prevalence of dementia of delayed age of dementia onset [11] or of a delayed progression from early stage to later stage of the disease [12]. Using multistate life tables, Wolters et al [13] evaluated the efficiency of scenarios of delayed onset of dementia

on life expectancies with and without dementia. However, none of these studies took into account the impact of the intervention on mortality.

To evaluate hypothetical interventions targeting risk factors of dementia while accounting for their impact on mortality, a method based on an illness-death model in continuous time was proposed [14, 15]. To allow the evaluation of more complex intervention scenarios targeting time-dependent risk factors, Jacqmin-Gadda et al [16] proposed a micro-simulation approach. This consists of the simulation of the life trajectories of a large number of individuals and then the computation of empirical estimates of indicators of disease burden. Although they are more computationally demanding than previous projection methods [11, 12, 15], micro-simulations are very flexible and were thus recommended for evaluating the impact of changes in the distribution of risk factors for dementia [17]. The micro-simulations approach was applied for forecasting the future burden of dementia in Canada [18] and in England [19] and for computing the associated health care cost. However, its use to evaluate hypothetical interventions targeting modifiable risk factors is scarce in the literature [20].

In the present work, we extend the micro-simulation algorithm proposed by Jacqmin-Gadda et al [16] to evaluate interventions targeting either simultaneously or independently three main vascular risk factors for dementia (diabetes, hypertension and physical inactivity) on the burden of dementia. Our models took into account both communality of the risk factors and their effect on mortality. We analyzed the impact of an intervention in France by 2040, and we made available an R package allowing to calculate these projections in different countries and for different scenarios of intervention.

Methods

Input data required

The Monte Carlo algorithm consists in simulating the life from age 65 of all the generations of subjects that will be aged between 65 and 105 at the target year for prediction (i.e. 2040). As mortality and dementia incidence, as well as the distribution of the vascular risk factors, are different between men and women, all the simulations were performed independently for men and women. Input data required for the simulations include age and sex-specific incidence of dementia and mortality with and without dementia according to the three risk factors considered. Hypertension and physical inactivity were considered fixed because the literature suggests that hypertension and physical inactivity at mid-life are risk factors for dementia [4]. For diabetes, both physiological hypotheses and epidemiological studies [7, 8] suggest that the onset of diabetes after age 65 could impact the risk of dementia. Thus diabetes was handled as a time-dependent risk factor. Consequently, the algorithm needs also the prevalence of the three risk factors at age 65 and the incidence of diabetes according to hypertension and physical inactivity after age 65.

Data Sources

The incidence and prevalence estimates needed for data generation were obtained either from preliminary estimation on a national database or large cohorts of elderly or from the literature when reliable estimates already existed. We selected or computed the estimated prevalences and incidences using representative samples as large as possible, and the estimated hazard ratios from cohorts with the best data on the risk factors.

Population sizes at age 65 and projections for general mortality in France by sex, age and calendar year were obtained from the French National Institute of Statistics and Economic Studies (INSEE).

Gender-specific prevalence at age 65 and incidence of treated diabetes from age 65 were provided by Fuentes et al. [21]. These estimations rely on the French National Health Data System which includes outpatient reimbursement of dispensed healthcare for the whole French population.

Incidence of dementia and hazard ratio of death with versus without dementia were estimated from the Paquid cohort. Paquid is a prospective cohort representative from two French departments that included 3777 subjects initially aged 65 years or over [22]. Subjects randomly selected from the electoral rolls who agreed to participate were interviewed at home by trained neuropsychologists at baseline in 1989 and subsequently every two or three years over 27 years. Diagnosis of dementia was assessed using DSM IIIR criteria in a two-phase procedure including screening by the neuropsychologist and a clinical examination at home by a neurologist. Vital status and exact date of death were collected all along the follow-up. Mortality in the Paquid cohort was shown to be very close to national mortality rate in France for the same period [14].

Communalities between risk factors and hazard ratio for incident diabetes according to hypertension and physical inactivity were estimated from the Three-City (3C) cohort [23]. This cohort included 9294 subjects living at home at inclusion in 3 French cities (Bordeaux, Dijon and Montpellier). They completed repeated interviews at 2,4,7, 10,12 and 14 years after the initial visit in 1999–2000 (except for the 4931 subjects from Dijon who had their last follow-up visit at 12 years). Hypertension was defined as diastolic blood pressure $\geq$ 140 mmHg or systolic blood pressure $\geq$ 90 mmHg using the mean of the two measures carried out at the baseline visit. Physical inactivity was defined as less than 1 hour per week of sport or recreational walking or intensive leisure activity. Incident diabetes was defined as the first occurrence of the use of antidiabetic drugs.

The hazard ratios for dementia and death associated with diabetes, hypertension, and physical inactivity were obtained from the largest recent studies we found in the literature. These parameters were assumed to be identical for men and women. Using a cohort of 155 000 subjects from 21 countries, Yusuf et al [24] estimated the adjusted hazard ratio for death associated with physical inactivity at 1.39 (1.28–1.50), with hypertension at 1.40 (1.31–1.50) and with diabetes at 1.68 (1.55–1.81). Based on several meta-analyses, Norton et al [6] reported relative risks for dementia equal to 1.82 (1.19–2.78) for physical inactivity, 1.61 (1.16–2.24) for hypertension and 1.46 (1.20–1.77) for diabetes. The hazard ratios for death in subjects with dementia were set at 1 because we considered that the potential excess risk associated with these risk factors was accounted for by the global excess risk of dementia subjects over non-dementia

subjects. This decision was supported by the nonsignificant associations observed in the 3C cohort between these three risk factors and the risk of death in dementia subjects.

Preliminary estimation:

From the above data, we estimated the incidence of dementia and the hazard ratio for death with dementia versus without dementia as well as the hazard ratios for incident diabetes according to hypertension and physical inactivity accounting for competing risk of death and interval censoring of dementia and diabetes. From these estimates and INSEE mortality projections, we obtained projections of mortality with and without dementia for future years. Then we estimated the prevalence of each combination of the risk factors at age 65 using nationwide prevalence of diabetes [21] and communality between risk factors from 3C. Methods for these preliminary estimations are detailed in the online supporting information.

Monte Carlo algorithm for projections in 2040

For each birth cohort aged between 65 and 105 in 2040, we generated the onset of diabetes, dementia and death from age 65 for a sample of 10 000 subjects alive and not demented at age 65 according to the algorithm detailed in online supporting information. Then, we computed empirical estimates of the prevalence of dementia, life-expectancy without dementia, life-long probability of dementia, mean age at dementia onset, and mean time spent with dementia.

Next, other runs of the simulation algorithm were performed under the intervention scenarios that assume a disappearance of the three risk factors from 2020 or of only one of the three risk factors. Variances of the estimates of epidemiological indicators were computed with 100 runs of the algorithm accounting for uncertainty on input parameters. As some studies suggest that the incidence of dementia has decreased over the 3 last decades [25], we performed a complementary set of simulations reducing the dementia incidence by 25%.

The Monte Carlo algorithm was implemented in the R package MCSPCD available at https://github.com/VivianePhilipps/MCSPCD.

Results

The online supporting information displays preliminary estimates used for the simulation algorithm. Age-specific incidence of dementia for men and women estimated on the Paquid cohort are shown in Supplementary Fig. 2. Supplementary Fig. 3 depicts the French mortality with and without dementia estimated for men and women by combining INSEE projections and Paquid estimates. The hazard ratios for dementia and death associated with the three risk factors are displayed in Supplementary Table 1. The estimated hazard ratios for diabetes associated with hypertension and physical inactivity are provided in Supplementary Table 2 and the mean incidence of diabetes by sex from Fuentes et al [21] is depicted in Supplementary Fig. 4. Finally, Supplementary Table 3 gives the prevalence at age 65 of all the combinations of the three risk factors.

Table 1 displays the estimated burden of dementia in 2040 assuming that the incidence of dementia remains identical to the incidence estimated in the Paquid cohort and in the hypothetical scenario of a disappearance of the three risk factors in 2020. Without intervention, the prevalence rate of dementia in 2040 would be 9.6% among men and 14.0% among women older than 65 and would decrease to 6.4% and 10.4%, respectively, under the intervention scenario. Figure 1 shows the age and sex-specific prevalence rates of dementia for the year 2040 with and without the intervention. The prevalence rates are significantly reduced for both men and women from age 75.

Table 1
– Monte Carlo estimates of indicators of dementia burden in France in 2040 assuming that the dementia incidence without intervention is stable and equal to the incidence estimated on the Paquid cohort and for the intervention scenario assuming the disappearance of hypertension, diabetes and physical inactivity from 2020.

	Men					
	Without intervention		With intervention		Difference	
	Value	95%CI	Value	95%CI	Value	95%CI
Prevalence rate (%)	9.56	[8.10, 11.02]	6.42	[4.73, 8.11]	-3.14	[-4.71 ,-1.57]
Lifelong proba (%)*	53.52	[48.63, 58.41]	45.84	[37.56, 54.12]	-7.68	[-14.80 ,-0.56]
Life expectancy without dementia§	20.12	[19.71, 20.54]	23.53	[22.46 ,24.61]	3.41	[2.38, 4.43]
Time in dementia§	3.29	[2.86, 3.71]	2.53	[1.93 ,3.13]	-0.75	[-1.28, -0.23]
Overall life expect.§	23.41	[23.36, 23.46]	26.06	[25.54, 26.58]	2.65	[2.11, 3.19]
Age at dementia onset§	82.42	[81.57, 83.27]	84.68	[83.55, 85.80]	2.25	[1.47, 3.03]
	Women					
	Without intervention		With intervention		Difference	
	Value	95%CI	Value	95%CI	Value	95%CI
Prevalence rate (%)	14.04	[12.51, 15.58]	10.42	[8.39, 12.45]	-3.63	[-5.22, -2.03]
Lifelong proba (%)*	69.73	[66.29, 73.17]	64.50	[59.14, 69.86]	-5.23	[-9.21, -1.25]
Life expectancy without dementia§	21.08	[20.65, 21.51]	23.67	[22.76, 24.58]	2.59	[1.79, 3.40]
Time in dementia§	5.09	[4.67, 5.51]	4.29	[3.68, 4.90]	-0.80	[-1.28, -0.33]
Overall life expect.§	26.17	[26.12, 26.22]	27.96	[27.61, 28.31]	1.79	[1.43, 2.15]

Abbreviations: 95%CI:95% confidence interval

* lifelong probability of dementia for a subject free of dementia at age 65

§ in years for a subject free of dementia at age 65.

	Men					
Age at dementia onset§	84.83	[84.15, 85.51]	86.71	[85.67, 87.76]	1.88	[1.11, 2.65]
Abbreviations: 95%CI:95% confidence interval						
* lifelong probability of dementia for a subject free of dementia at age 65						
§ in years for a subject free of dementia at age 65.						

While the intervention would decrease the prevalence rate in 2040 by about 33% among men and 26% among women, the relative decrease of the lifelong probability of dementia for a subject free of dementia at age 65 would be only 14.3% (from 53.5–45.8%) among men and 7.5% among women (from 69.7–64.5%). The impact on the lifelong probability is smaller because of the increase in the overall life expectancy (+ 2.65 years in men and + 1.79 years in women) since the three targeted risk factors are also associated with mortality. Due to the effect on both mortality and incidence of dementia, the intervention would result in a gain of 3.4 years of life expectancy without dementia for men aged 65 years, and 2.6 years for women. For the year 2040, the mean age at dementia onset would increase from 82.4 years without intervention to 84.7 years with the intervention in men and from 84.8 to 86.7 years in women. Overall, the intervention would have a larger impact on the burden of dementia among men because the prevalence of exposure to at least one of the cardiovascular risk factors considered and the incidence of diabetes are higher among men (see Supplementary Table 3 and Supplementary Fig. 4).

Table 2 displays the simulation results assuming that the baseline incidence is reduced by 25% compared to the incidence of Paquid. With this incidence, the prevalence rates would be only 7.1% among men and 10.7% among women in 2040. These figures would drop to 4.7% and 7.7% in case of intervention. The mean age at dementia onset is only slightly impacted by the overall reduction of dementia incidence. On the contrary, the lifelong probability of dementia is reduced by about 10 points compared to Table 1 both with and without intervention. Without intervention, the life expectancy without dementia is 0.9 years higher in men and 1.2 years higher in women due to the overall reduction of dementia incidence, while the mean time spent with dementia decreases by a similar amount. Overall, while considering the 25% reduction of dementia incidence reduces the global burden of dementia in 2040 it has little impact on the effect of the intervention: targeting the three modifiable risk factors would be similar to the first set of simulations.

Table 2
– Monte Carlo estimates of indicators of dementia burden in France in 2040 assuming that the dementia incidence without intervention is stable and reduced by 25% compared the incidence estimated on the Paquid cohort and for the intervention scenario assuming disappearance of hypertension, diabetes and physical inactivity from 2020.

	Men					
	Without intervention		With intervention		Difference	
	Value	95%CI*	Value	95%CI	Value	95%CI
Prevalence rate (%)	7.11	[5.71, 8.51]	4.67	[3.06, 6.29]	-2.44	[-3.94, -0.93]
Lifelong proba (%)*	43.44	[38.78, 48.10]	36.02	[28.02, 44.02]	-7.42	[-14.33, -0.51]
Life expectancy without dementia§	20.99	[20.57, 21.41]	24.42	[23.40, 25.44]	3.43	[2.47, 4.40]
Time in dementia§	2.42	[2.04, 2.81]	1.81	[1.26, 2.36]	-0.61	[-1.10, -0.13]
Overall life expect.§	23.41	[23.31, 23.52]	26.23	[25.73, 26.74]	2.82	[2.30, 3.34]
Age at dementia§	82.66	[81.82, 83.51]	85.03	[83.91, 86.15]	2.37	[1.57, 3.16]
	Women					
	Without intervention		With intervention		Difference	
	Value	95%CI	Value	95%CI	Value	95%CI
Prevalence rate (%)	10.66	[9.17, 12.14]	7.66	[5.72, 9.60]	-3.00	[-4.52, -1.48]
Lifelong proba (%)*	59.86	[56.60, 63.12]	53.53	[48.29, 58.77]	-6.33	[-10.40, -2.26]
Life expectancy without dementia§	22.26	[21.84, 22.69]	24.89	[24.01, 25.76]	2.62	[1.85, 3.40]
Time in dementia§	3.92	[3.51, 4.32]	3.23	[2.65, 3.81]	-0.68	[-1.13, -0.24]
Overall life expect.§	26.18	[26.08, 26.28]	28.12	[27.77, 28.46]	1.94	[1.59, 2.29]

Abbreviations: 95%CI:95% confidence interval

* lifelong probability of dementia for a subject free of dementia at age 65

§ in years for a subject free of dementia at age 65.

	Men					
Age at dementia§	85.34	[84.66, 86.01]	87.28	[86.23, 88.33]	1.94	[1.19, 2.69]
Abbreviations: 95%CI:95% confidence interval						
* lifelong probability of dementia for a subject free of dementia at age 65						
§ in years for a subject free of dementia at age 65.						

Tables 3, 4 and 5 present simulation results for intervention scenarios targeting only one of the three modifiable risk factors. In the hypothetical scenario of the disappearence of hypertension (Table 3), the relative decrease of dementia prevalence rates in 2040 would be 21.4% in men and only 15.6% in women due to their lower hypertension prevalence. This would be associated with, respectively, a 10% and 4.3% decrease in the lifelong probability of dementia among men and women and a gain in life expectancy without dementia of 2 years in men and 1.4 years in women. As the prevalences of diabetes and physical inactivity are much lower than hypertension, interventions targeting only one of these factors would have less impact on the dementia burden. The disappearance of diabetes (Table 4) would decrease dementia prevalence rates by 6.2% in men and 4.2% in women but the change in lifelong probability of dementia and time spent in dementia would be almost null because of the increase in the overall life expectancy. Indeed, the HR for mortality associated with diabetes is higher than the one for dementia (see S-Table 1). An intervention targeting physical inactivity only would have also a modest impact on dementia burden but still with an impact on the lifelong probability of dementia since the effect of physical inactivity on mortality is assumed to be lower than on dementia (according to [6] and [24], see Supplementary Table 1). Moreover, physical inactivity being more frequent in women, this intervention would reduce further the burden of dementia in women.

Table 3

Monte Carlo estimates of indicators of dementia burden in France in 2040 assuming that the dementia incidence without intervention is stable and equal to the incidence estimated on the Paquid cohort and for the intervention scenario assuming only disappearance of hypertension.

	Men					
	Without intervention		With intervention		Difference	
	Value	95%CI*	Value	95%CI	Value	95%CI
Prevalence rate (%)	9.56	[8.10, 11.02]	7.51	[5.73, 9.29]	-2.05	[-3.69, -0.40]
Lifelong proba (%)*	53.52	[48.63, 58.41]	48.09	[40.35, 55.83]	-5.43	[-12.04, 1.18]
Life expectancy without dementia§	20.12	[19.71, 20.54]	22.12	[21.13, 23.11]	1.99	[1.03, 2.96]
Time in dementia§	3.29	[2.86, 3.71]	2.81	[2.22, 3.40]	-0.48	[-1.00, 0.05]
Overall life expect.§	23.41	[23.36, 23.46]	24.93	[24.47, 25.38]	1.52	[1.04, 1.99]
Age at dementia§	82.42	[81.57, 83.27]	83.82	[82.82, 84.83]	1.40	[0.72, 2.07]
	Women					
	Without intervention		With intervention		Difference	
	Value	95%CI	Value	95%CI	Value	95%CI
Prevalence rate (%)	14.04	[12.51, 15.58]	12.01	[9.88, 14.13]	-2.04	[-3.57, -0.51]
Lifelong proba (%)*	69.73	[66.29, 73.17]	66.75	[61.86, 71.64]	-2.98	[-6.35, 0.39]
Life expectancy without dementia§	21.08	[20.65, 21.51]	22.47	[21.61, 23.33]	1.39	[0.65, 2.13]
Time in dementia§	5.09	[4.67, 5.51]	4.66	[4.05, 5.27]	-0.43	[-0.87, 0.02]
Overall life expect.§	26.17	[26.12, 26.22]	27.13	[26.83, 27.44]	0.96	[0.64, 1.28]

Abbreviations: 95%CI:95% confidence interval

* lifelong probability of dementia for a subject free of dementia at age 65

§ in years for a subject free of dementia at age 65.

	Men					
Age at dementia§	84.83	[84.15, 85.51]	85.78	[84.79, 86.76]	0.94	[0.27, 1.62]
Abbreviations: 95%CI:95% confidence interval						
* lifelong probability of dementia for a subject free of dementia at age 65						
§ in years for a subject free of dementia at age 65.						

Table 4

Monte Carlo estimates of indicators of dementia burden in France in 2040 assuming that the dementia incidence without intervention is stable and equal to the incidence estimated on the Paquid cohort and for the intervention scenario assuming only disappearance of diabetes.

	Men					
	Without intervention		With intervention		Difference	
	Value	95%CI*	Value	95%CI	Value	95%CI
Prevalence rate (%)	9.56	[8.10, 11.02]	8.97	[7.47, 10.48]	-0.59	[-1.03, -0.14]
Lifelong proba (%)*	53.52	[48.63, 58.41]	53.37	[48.07, 58.67]	-0.15	[-2.17, 1.87]
Life expectancy without dementia§	20.12	[19.71, 20.54]	20.94	[20.36, 21.51]	0.81	[0.55, 1.07]
Time in dementia§	3.29	[2.86, 3.71]	3.27	[2.80, 3.75]	-0.01	[-0.17, 0.15]
Overall life expect.§	23.41	[23.36, 23.46]	24.21	[24.05, 24.37]	0.80	[0.64, 0.96]
Age at dementia§	82.42	[81.57, 83.27]	82.95	[82.10, 83.81]	0.53	[0.33, 0.72]
	Women					
	Without intervention		With intervention		Difference	
	Value	95%CI	Value	95%CI	Value	95%CI
Prevalence rate (%)	14.04	[12.51, 15.58]	13.46	[11.95, 14.97]	-0.59	[-1.01, -0.16]
Lifelong proba (%)*	69.73	[66.29, 73.17]	69.73	[66.33, 73.13]	0.00	[-1.18, 1.18]
Life expectancy without dementia§	21.08	[20.65, 21.51]	21.62	[21.13, 22.10]	0.54	[0.35, 0.72]
Time in dementia§	5.09	[4.67, 5.51]	5.01	[4.56, 5.46]	-0.08	[-0.22, 0.06]
Overall life expect.§	26.17	[26.12, 26.22]	26.63	[26.53, 26.73]	0.46	[0.37, 0.55]

Abbreviations: 95%CI:95% confidence interval

* lifelong probability of dementia for a subject free of dementia at age 65

§ in years for a subject free of dementia at age 65.

	Men					
Age at dementia§	84.83	[84.15, 85.51]	85.08	[84.36, 85.81]	0.25	[0.05, 0.46]
Abbreviations: 95%CI:95% confidence interval						
* lifelong probability of dementia for a subject free of dementia at age 65						
§ in years for a subject free of dementia at age 65.						

Table 5

Monte Carlo estimates of indicators of dementia burden in France in 2040 assuming that the dementia incidence without intervention is stable and equal to the incidence estimated on the Paquid cohort and for the intervention scenario assuming only disappearance of physical inactivity.

	Men					
	Without intervention		With intervention		Difference	
	Value	95%CI*	Value	95%CI	Value	95%CI
Prevalence rate (%)	9.56	[8.10, 11.02]	8.92	[7.45, 10.39]	-0.64	[-1.15, -0.12]
Lifelong proba (%)*	53.52	[48.63, 58.41]	51.74	[46.45, 57.03]	-1.78	[-3.62, 0.06]
Life expectancy without dementia§	20.12	[19.71, 20.54]	20.59	[20.07, 21.12]	0.47	[0.19, 0.75]
Time in dementia§	3.29	[2.86, 3.71]	3.19	[2.73, 3.66]	-0.09	[-0.26, 0.08]
Overall life expect.§	23.41	[23.36, 23.46]	23.79	[23.69, 23.89]	0.38	[0.24, 0.52]
Age at dementia§	82.42	[81.57, 83.27]	82.78	[81.93, 83.63]	0.35	[0.07, 0.63]
	Women					
	Without intervention		With intervention		Difference	
	Value	95%CI	Value	95%CI	Value	95%CI
Prevalence rate (%)	14.04	[12.51, 15.58]	13.01	[11.42, 14.61]	-1.03	[-1.82, -0.24]
Lifelong proba (%)*	69.73	[66.29, 73.17]	68.24	[64.51, 71.97]	-1.49	[-3.09, 0.11]
Life expectancy without dementia§	21.08	[20.65, 21.51]	21.71	[21.17, 22.24]	0.63	[0.28, 0.97]
Time in dementia§	5.09	[4.67, 5.51]	4.89	[4.41, 5.36]	-0.21	[-0.44, 0.03]
Overall life expect.§	26.17	[26.12, 26.22]	26.59	[26.45, 26.73]	0.42	[0.28, 0.56]

Abbreviations: 95%CI:95% confidence interval

* lifelong probability of dementia for a subject free of dementia at age 65

§ in years for a subject free of dementia at age 65.

	Men					
Age at dementia§	84.83	[84.15, 85.51]	85.21	[84.45, 85.98]	0.38	[0.01, 0.76]
Abbreviations: 95%CI:95% confidence interval						
* lifelong probability of dementia for a subject free of dementia at age 65						
§ in years for a subject free of dementia at age 65.						

Discussion

This study shows that fighting against hypertension, diabetes and physical inactivity could reduce the prevalence of dementia in 2040 in France by as much as 33% in men and 26% in women and would increase life expectancy without dementia at age 65 of 3.4 years in men and 2.6 years in women. This impact would be higher in men because they are more frequently exposed to these risk factors (currently 76% of men versus 60% of women have at least one of these risk factors at age 65). Among the three factors, hypertension has the largest impact on dementia burden since this is, by far, the most prevalent (69% in men and 49% in women). The disappearance of hypertension alone could decrease dementia prevalence by 21% in men and 16% in women while intervention targeting only diabetes or physical inactivity would lead to a reduction in dementia prevalence of only 4–7%. In the case of disappearance of diabetes, due to a fairly high reduction in mortality in parallel with the reduction in dementia prevalence, the lifelong probability of dementia and the mean time spent in dementia would not change in this scenario.

The proposed methodology has major assets. First, unlike previously published evaluation of intervention scenarios on dementia burden [11, 12, 13] or computation of attributable risk for some risk factors [6, 10], it accounts for the impact of change in risk factors distribution on mortality. This is an essential issue since most modifiable risk factors of dementia are also associated with mortality which is indeed the major competing risk of dementia in the elderly. The methods also account for the frequent co-exposure of elderly subjects to 2 or 3 risk factors. Moreover, the Monte-Carlo approach makes possible to forecast the impact of intervention scenarios on many indicators of the disease burden. Finally, the algorithm allows computing confidence intervals for the predictions accounting for the variances of the estimates of the input parameters when they are known.

At first glance, the scenarios assessed could appear too optimistic since we assumed a total disappearance of the risk factors. However, the first objective of this kind of approach is to provide alternative measures to the attributable risk to quantify the impact of exposures, alone or combined, on a disease accounting for their effect on mortality. From a Public Health perspective, our scenarios provide the magnitude of the maximum change that can be expected in dementia burden from efficient interventions targeting the considered risk factors and highlight the contribution of each factor. Given these assessments rely on previous estimations of many input parameters (the dementia incidence, the

hazard ratios, the prevalence of exposures,…) subject to uncertainty, we think it is more meaningful to quantify the variance of the predictions rather than to refine the intervention scenarios. Nevertheless, the methods have been implemented in an R-package freely available that can be used for testing different scenarios or evaluating the impact of other risk factors or other diseases.

To our knowledge, only one study evaluated the impact of interventions targeting vascular risk factors on dementia burden while accounting for their impact on mortality [20]. Using a micro-simulations model for a birth cohort, Zissimopoulos et al. [20] estimated that hypertension disappearance and reduction of diabetes would have a lower impact on the burden of dementia in the United States than what we found. Indeed, they found a slight increase of years spent with dementia and lifetime risk of dementia due to an increase of the overall life expectancy. The main reason for this difference is probably the values of the input parameters for the association of diabetes and hypertension with dementia and death. The association parameters for dementia used in Zissimopoulos et al. were very low and thus probably lower than the association parameters for death (which are not given in their article). In addition, we assumed that the intervention does not modify the mortality with dementia which is probably not the case in Zissimopoulos et al. [20]. We previously showed that the relative values of the hazard ratios for dementia and death were the most influential on the impact of intervention modifying the risk factor prevalence [26].

As all projection studies evaluating the impact of a decrease in risk factors prevalence, this study relies on the assumption of a causal effect of hypertension, diabetes and physical inactivity on dementia, which is still debated. However, we selected modifiable risk factors for which there is convincing evidence of a strong association with dementia based on longitudinal studies fulfilling the temporality criterion for causality [4]. Moreover, studies support a reduction of brain volume and an increase of white matter hyperintensities in hypertension patients [27] while cognitive dysfunctions in patients with diabetes could involve several mechanisms including vascular complications [28, 29].

Finally, it is useful to note that our estimates of life expectancies (overall or without dementia) are different from standard estimates in demography. The demographs compute life expectancy using only mortality and incidence estimates from the target year (2040) while we simulate the life expectancy of subjects aged 65 in 2040 accounting for the evolution of mortality in the next years. Due to the decreasing trend of mortality over years, our estimate is expected to be larger than standard estimates.

Relying on current estimates of the (assumed causal) effects of vascular risk factors on dementia and death, this study shows that interventions aiming at decreasing the prevalence of these modifiable risk factors could be an efficient way to reduce the future burden of dementia. Since such interventions would also increase the overall life expectancy and consequently the size of the oldest population, which is at the highest risk of dementia, the expected change in the various measures of dementia burden highly depends on the relative effect on dementia incidence and mortality. Using the methodology made available in the R package MCSPCD, the projections can be adapted for different countries according to

the mortality rate and refined when updated estimates of the relative effect on dementia incidence and mortality will be available.

Declarations

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Author contributions

H.J.-G. and P.J. conceived, designed and supervised the research. H.J.-G wrote the original draft. F.G. and V.P. implemented the R code and performed the simulations. C.H. provided the Paquid data and contributed to the analysis of Paquid data. C.T. and C.H. provided the 3C data and contributed to their analysis. All authors contributed to the interpretation of the results, revised the paper and approved the final manuscript.

Competing interests:

The authors declare no competing interests.

Ethics approval:

The Paquid protocol was approved by the Ethics Committee of the Bordeaux University Hospital The 3C protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and Sud-

Mediterranée III.

Each participant provided signed informed consent.

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Figures

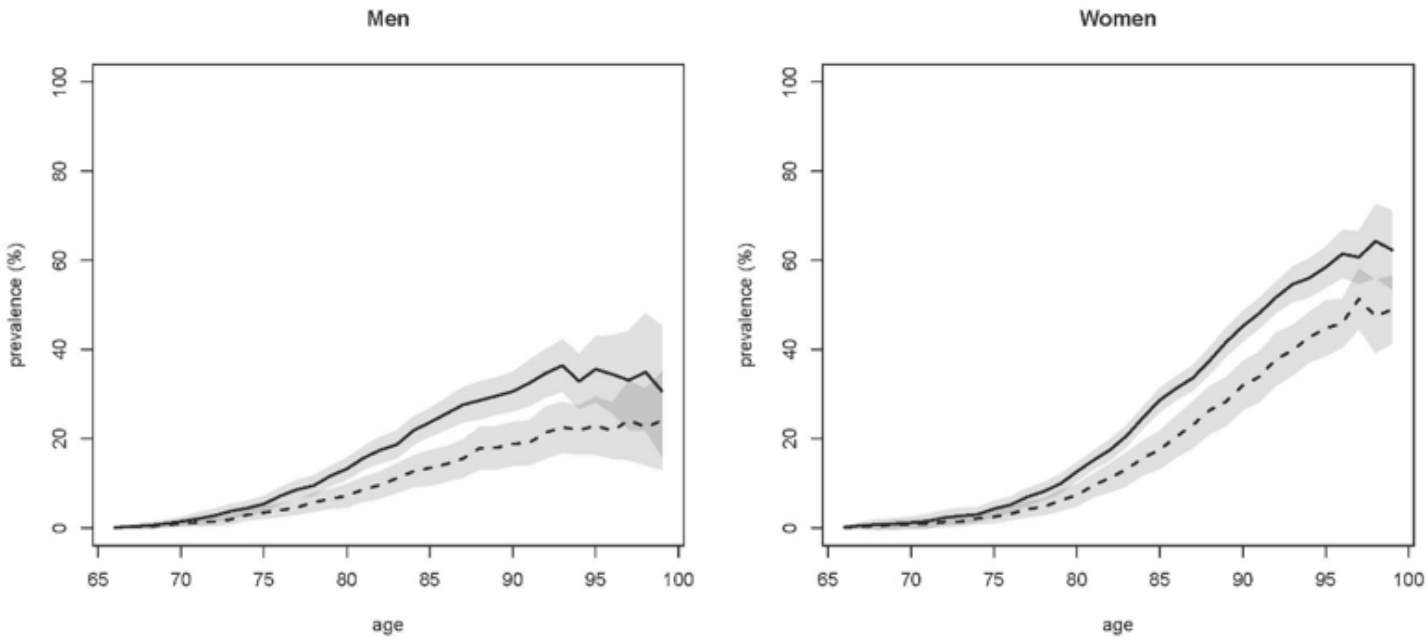

Figure 1

Age-and gender-specific prevalence rates of dementia for the year 2040 with (dashed-line) and without (plain line) the intervention with 95% confidence-intervals (grey shadow).

Supplementary Files

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