

Supplementary material

Analytic epidemiology approach

To estimate the association between explanatory variables and the event of interest, the influence of potentially confounding covariates should be taken into account by adjusting statistical models on these covariates. Confounding bias occurs when a third factor distorts the measure of association because that factor is associated with both the exposure and the event of interest. Under correct causal assumptions, statistical adjustment can prevent such bias. Therefore, analytic epidemiological approach aims to establish adjustment sets for causal analysis, with should be both exhaustive, in order to limit confounding bias risk, and parsimonious, to limit the loss of statistical power associated with unnecessary adjustments (1). This careful attention to covariates in modelling is also intended to avoid over-adjustment bias, which can distort associations' estimations, if adjustment is applied improperly on a collider, rather than on a real confounder (2). For older adults population, this concern for correct adjustment is particularly relevant, as clinical and sociodemographic factors are interrelated (3-6).

Thus, our analytic approach first consisted in reviewing literature to identify covariates of interest that may be associated with either explanatory factors or event of interest. This review was extended to all the covariates identified in the literature. Then, directed acyclic graphs (DAG) were built, allowing a visual representation of the causal relationships between variables, and providing a minimal adjustment for association analysis (7). On these graphs, an arrow indicates a causal link between two variables (e.g., Initial unfavourable tumour prognosis → Death). The logical temporal sequence "cause → effect" must be respected for a causal link to exist. The omission of an arrow implies the certainty that there is no causal link between two variables, which may be a strong assumption. Each causal hypothesis were reviewed and confirmed by expert committee, who also intended to identify any variable whose effect may be mediated by others. Variables identified in literature but unavailable from patient's follow-up were excluded. Final DAGs representing variables potential causal links were produced with DAGitty software (7), and used for modelling association between retained explanatory variables and HPC referral.

Assumptions of causation

Comprehensive literature analysis provided exhaustive identification of factors that might influence HPC referral in older adults population, whether they be socio-demographic, tumor-related, or geriatric factors. Among them, malnutrition, multi-morbidity and ethnicity variables were not collected in cohorts follow-up or cancer registries. For multi-morbidity, a polypharmacy proxy variable was used. The potential effect of malnutrition on explanatory variables or outcome was assumed being mediated by this same proxy variable. Ethnic data collection in France and European Union is restricted to specific indications, and was not available. Yet, ethnicity's potential association with HPC referral was assumed being mediated by other sociodemographic variables reflecting precariousness and isolation, such as socio-professional category, household income, or social isolation. The expert committee retained other effects mediations: socio-professional category over active life mediated household income. The way of living (alone or surrounded) mediated the effect of living in nursing homes.

Covariates choice

Expert committee's evaluation retained the following adjustment hypothesis for modelling HPC referral's determinants (8-56).

Concerning the effect of age at diagnosis on HPC referral, sociodemographic variables (gender, socio-professional category, place of residency and the way of living) were assumed to influence age at diagnosis, as well as geriatric factors (cognitive impairment – MMSE, functional limitations to ADL/IADL, polypharmacy, and depression disorders – CESD). All these variables were retained for adjustment set in modelling.

Sociodemographic variables, geriatric factors, and tumour prognosis were considered as being influenced by gender. Under hypothesis that these variables might be intermediate factors between gender and HPC referral, modelling remained univariate for estimations of HPC referral Hazard Ratios.

Concerning the place of residency during cohort follow-up (rural vs urban), age at diagnosis was not retained for adjustment. Gender, socio-professional category, limitations at IADL/ADL, cognitive impairment, and polypharmacy might influence the place of residency, as well as HPC referral. They were included as adjustment covariates.

For the fact of living alone before cancer diagnosis, gender, place of residency, socio-demographic category, and geriatric factors were retained as adjustment covariates.

Concerning the initial tumour prognosis, age at diagnosis, patient's gender, and all socio-demographic and geriatric variables were considered as covariates for adjustment. Indeed, these factors may influence either the type of cancer, and cause a delayed diagnosis, with more advanced tumours on the loco-regional basis or with metastasis.

For all geriatric factors, gender, socio-professional category, and polypharmacy were retained as adjustment covariates. For depressive disorders, place of residency, living alone, and functional or cognitive impairments were also retained, considering that they might affect both explanatory variable and outcome.

From these hypothesis, one DAG was built for each one of the ten explanatory variable. Complete DAGs are not presented here due to their poor legibility, but simplified DAGs for gender and functional limitations to IADL or ADL are proposed as examples (Figures S1 and S2).

Table S1. Assumptions of causation assumed by the expert committee, PACPAL Study

Relations	Assumptions
Age at diagnosis – HPC Referral	Age at diagnosis might affect HPC referral (8-10)
Gender – HPC Referral	Gender might affect HPC referral (8-9,11)
Initial tumour prognosis – HPC Referral	Initial tumour prognosis might affect HPC referral (8-12)
Living alone – HPC Referral	Living alone might affect HPC referral (13-14)
Place or residence – HPC Referral	Place of residence might affect HPC referral (13)
Cognitive impairment – HPC Referral	Cognitive impairment might affect HPC referral (15)
Functional limitations – HPC Referral	Functional limitations (ADL, IADL) might affect HPC referral (16-17)
Depressive disorders – HPC Referral	Depressive disorders might affect HPC referral (17-18)
Polypharmacy (multi-morbidity) – HPC Referral	Polypharmacy (multi-morbidity) might affect HPC referral (5,19)
Age at diagnosis – Gender	Gender might affect age at diagnosis
Age at diagnosis – Socio-professional category	Socio-professional category might affect age at diagnosis (20)
Age at diagnosis – Ethnicity*	Ethnicity* might affect age at diagnosis (20-21)
Age at diagnosis – Living alone	Living alone might affect age at diagnosis (20)
Age at diagnosis – Living in nursing homes	Living in nursing homes might affect age at diagnosis
Age at diagnosis – Household income	Household income might affect age at diagnosis (20)
Age at diagnosis – Place of residency	Place of residency might affect age at diagnosis (20)
Age at diagnosis – Functional limitations	Functional limitations might affect age at diagnosis (22-25)
Age at diagnosis – Depressive disorders	Depressive disorders might affect age at diagnosis (26)
Age at diagnosis – Cognitive impairment	Cognitive impairment might affect age at diagnosis (27)
Age at diagnosis – Polypharmacy (multi-morbidity)	Polypharmacy might affect age at diagnosis (28)
Age at diagnosis – Malnutrition*	Malnutrition* might affect age at diagnosis (29)
Age at diagnosis – Initial tumour prognosis	Age at diagnosis might affect initial tumour prognosis (30)
Gender – Age at diagnosis	No effect
Gender – Socio-professional category	Gender might affect socio-professional category (31)
Gender – Ethnicity*	No effect
Gender – Living alone	Gender might affect the way of living (32)
Gender – Living in nursing homes	Gender might affect the fact of living in nursing homes (33)
Gender – Household income	Gender might affect household income (31)
Gender – Place of residency	No effect
Gender – Functional limitations	Gender might affect the existence of functional limitations (34)
Gender – Depressive disorders	Gender might affect the existence of depressive disorders (35)
Gender – Cognitive impairment	Gender might affect the existence of cognitive impairment (36)
Gender – Polypharmacy (multi-morbidity)	Gender might affect the existence of polypharmacy (37)
Gender – Malnutrition*	Gender might affect the existence of malnutrition* (38)
Gender – Initial tumour prognosis	Gender might affect initial tumour prognosis (30)
Living alone – Age at diagnosis	Living alone might affect age at diagnosis (20)
Living alone – Gender	Gender might affect the way of living alone or surrounded (32)
Living alone – Socio-professional category	Socio-professional category might affect the way of living
Living alone – Ethnicity*	Ethnicity* might affect the way of living alone or not
Living alone – Living in nursing homes	Living alone might affect the fact of living in nursing homes (39)
Living alone – Household income	Living alone might affect household income
Living alone – Place of residency	Place of residency might affect the way of living (40)
Living alone – Functional limitations	Functional limitations might affect the way of living
Living alone – Depressive disorders	Living alone might affect the existence of depressive disorders (41)
Living alone – Cognitive impairment	Existence of cognitive impairment might affect the way of living (42)
Living alone – Polypharmacy (multi-morbidity)	Existence of polypharmacy might affect the way of living
Living alone – Malnutrition*	Existence of malnutrition* might affect the way of living (43)
Living alone – Initial tumour prognosis	Living alone might affect initial tumour prognosis (44)

* = unavailable variables in cohorts follow-up/cancer-registries ; IADL = Instrumental Activities of Daily Living ; ADL = Activities of Daily Living

Table S1. Assumptions of causation assumed by the expert committee, PACPAL Study (cont.)

Relations	Assumptions
Place of residency – Age at diagnosis	Place of residency might affect age at diagnosis (20)
Place of residency – Gender	No effect
Place of residency – Socio-professional category	Socio-professional category might affect the place of residency (40)
Place of residency – Ethnicity*	Ethnicity* might affect the place of residency
Place of residency – Living in nursing homes	Place of residency might affect the fact of living in nursing homes (40)
Place of residency – Living alone	Place of residency might affect the way of living (39)
Place of residency – Household income	Household income might affect the place of residency
Place of residency – Functional limitations	No effect
Place of residency – Depressive disorders	Place of residency might affect existence of depressive disorders (35)
Place of residency – Cognitive impairment	No effect
Place of residency – Polypharmacy (multi-morbidity)	No effect
Place of residency – Malnutrition*	No effect
Place of residency – Initial tumour prognosis	Place of residency might affect initial tumour prognosis (44)
Initial tumour prognosis – Age at diagnosis	Age at diagnosis might affect initial tumour prognosis (30)
Initial tumour prognosis – Gender	Gender might affect initial tumour prognosis (30-45)
Initial tumour prognosis – Socio-professional category	Socio-professional category might affect initial tumour prognosis (42)
Initial tumour prognosis – Ethnicity*	Ethnicity* might affect initial tumour prognosis (46)
Initial tumour prognosis – Living in nursing homes	Living in nursing homes might affect initial tumour prognosis (47)
Initial tumour prognosis – Living alone	Living alone might affect initial tumour prognosis (47)
Initial tumour prognosis – Place of residency	Place of residency might affect initial tumour prognosis (44)
Initial tumour prognosis – Household income	Household income might affect initial tumour prognosis (46)
Initial tumour prognosis – Functional limitations	Functional limitations might affect initial tumour prognosis (48)
Initial tumour prognosis – Depressive disorders	Depressive disorders might affect initial tumour prognosis (26)
Initial tumour prognosis – Cognitive impairment	Cognitive impairment might affect initial tumour prognosis (27)
Initial tumour prognosis – Polypharmacy (multi-morbidity)	Polypharmacy might affect initial tumour prognosis (28)
Initial tumour prognosis – Malnutrition*	Malnutrition* might affect initial tumour prognosis (28)
Functional limitations – Age at diagnosis	Functional limitations might affect age at diagnosis (22-25)
Functional limitations – Gender	Gender might affect existence of functional limitations (34)
Functional limitations – Socio-professional category	Socio-professional category might affect functional limitations (49)
Functional limitations – Ethnicity*	Ethnicity* might affect functional limitations (50)
Functional limitations – Living in nursing homes	Functional limitations might affect living in nursing homes (51)
Functional limitations – Living alone	Functional limitations might affect the way of living
Functional limitations – Place of residency	No effect
Functional limitations – Household income	Functional limitations might affect household income (52)
Functional limitations – Depressive disorders	Depressive disorders might affect functional limitations (35)
Functional limitations – Cognitive impairment	Cognitive impairment might affect functional limitations (34,49)
Functional limitations – Polypharmacy (multi-morbidity)	Polypharmacy might affect functional limitations (53)
Functional limitations – Malnutrition*	Malnutrition* might affect functional limitations (38)
Functional limitations – Initial tumour prognosis	Functional limitations might affect initial tumour prognosis (48)

* = unavailable variables in cohorts follow-up/cancer-registries ; IADL = Instrumental Activities of Daily Living ; ADL = Activities of Daily Living

Table S1. Assumptions of causation assumed by the expert committee, PACPAL Study (cont.)

Relations	Assumptions
Depressive disorders – Age at diagnosis	Depressive disorders might affect age at diagnosis (26)
Depressive disorders – Gender	Gender might affect existence of depressive disorders (35)
Depressive disorders – Socio-professional category	Socio-professional category might affect depressive disorders (26)
Depressive disorders – Ethnicity*	Ethnicity* might affect depressive disorders (41)
Depressive disorders – Living in nursing homes	Living in nursing homes might affect depressive disorders (41)
Depressive disorders – Living alone	Way of living might affect depressive disorders (41)
Depressive disorders – Place of residency	Place of residency might affect depressive disorders (35)
Depressive disorders – Household income	Household income might affect depressive disorders (26)
Depressive disorders – Functional limitations	Depressive disorders might affect functional limitations (35)
Depressive disorders – Cognitive impairment	Cognitive impairment might affect depressive disorders (41)
Depressive disorders – Polypharmacy (multi-morbidity)	Polypharmacy might affect depressive disorders (53)
Depressive disorders – Malnutrition*	Depressive disorders might affect malnutrition* (53)
Depressive disorders – Initial tumour prognosis	Depressive disorders might affect initial tumour prognosis (26)
Cognitive impairment – Age at diagnosis	Cognitive impairment might affect age at diagnosis (34,49)
Cognitive impairment – Gender	Gender might affect the existence of cognitive impairment (36)
Cognitive impairment – Socio-professional category	Socio-professional category may affect cognitive impairment (42)
Cognitive impairment – Ethnicity*	Ethnicity* might affect cognitive impairment (42)
Cognitive impairment – Living in nursing homes	Cognitive impairment might affect living in nursing homes (42)
Cognitive impairment – Living alone	Functional limitations might affect the way of living (42)
Cognitive impairment – Place of residency	No effect
Cognitive impairment – Household income	Cognitive impairment might affect household income (54)
Cognitive impairment – Depressive disorders	Cognitive impairment might affect depressive disorders (55)
Cognitive impairment – Functional limitations	Cognitive impairment might affect functional limitations (34,49)
Cognitive impairment – Polypharmacy (multi-morbidity)	Cognitive impairment might affect polypharmacy (56)
Cognitive impairment – Malnutrition*	Cognitive impairment might affect malnutrition* (29)
Cognitive impairment – Initial tumour prognosis	Cognitive impairment might affect initial tumour prognosis (38)
Polypharmacy (multi-morbidity) – Age at diagnosis	Polypharmacy might affect age at diagnosis (28)
Polypharmacy (multi-morbidity) – Gender	Gender might affect existence of polypharmacy (37)
Polypharmacy (multi-morbidity) – Socio-professional category	Socio-professional category might affect polypharmacy (56)
Polypharmacy (multi-morbidity) – Ethnicity*	Ethnicity* might affect polypharmacy (56)
Polypharmacy (multi-morbidity) – Living in nursing homes	Polypharmacy might affect living in nursing homes (56)
Polypharmacy (multi-morbidity) – Living alone	Polypharmacy might affect the way of living
Polypharmacy (multi-morbidity) – Place of residency	No effect
Polypharmacy (multi-morbidity) – Household income	Polypharmacy might affect household income
Polypharmacy (multi-morbidity) – Depressive disorders	Polypharmacy might affect depressive disorders (41)
Polypharmacy (multi-morbidity) – Cognitive impairment	Cognitive impairment might affect polypharmacy (56)
Polypharmacy (multi-morbidity) – Functional limitations	Polypharmacy might affect functional limitations (53)
Polypharmacy (multi-morbidity) – Malnutrition*	Polypharmacy might affect malnutrition (38)
Polypharmacy (multi-morbidity) – Initial tumour prognosis	Polypharmacy might affect initial tumour prognosis (29)

* = unavailable variables in cohorts follow-up/cancer-registries ; IADL = Instrumental Activities of Daily Living ; ADL = Activities of Daily Living

Table S2. Minimally sufficient adjustment sets retained (shaded cells) after relationships analysis for HPC referral determinants, PACPAL study

Explanatory Variable	Covariates									
	Age ^a	Gender ^a	Urban/rural place of residence ^a	Living alone or surrounded ^a	Tumour prognosis ^a	IADL, ADL ^b	MMSE ^b	CESD ^b	Polypharmacy, proxy for multi-morbidity ^b	SCP during life
Age ^a	NA									
Gender ^a		NA								
Urban/rural place of residency ^a			NA							
Living alone or surrounded ^a				NA						
Tumour prognosis ^a					NA					
IADL, ADL ^b						NA				
MMSE ^b							NA			
CESD ^b								NA		
Polypharmacy, proxy for multi-morbidity ^b									NA	

NA = Not applicable, this variable being the variable of interest in this model

^a Variables measured at cancer diagnosis

IADL = Instrumental activities of daily living

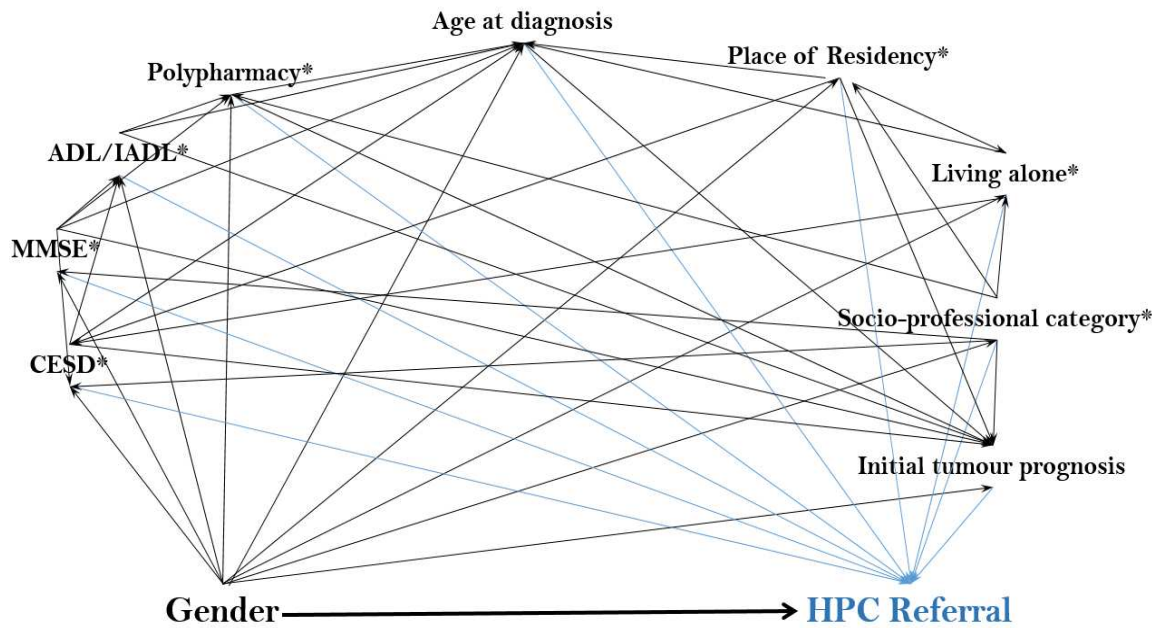
^b Variables measured before cancer diagnosis, during cohort follow-up

ADL = Activities of daily living

MMSE = Mental-state score examination

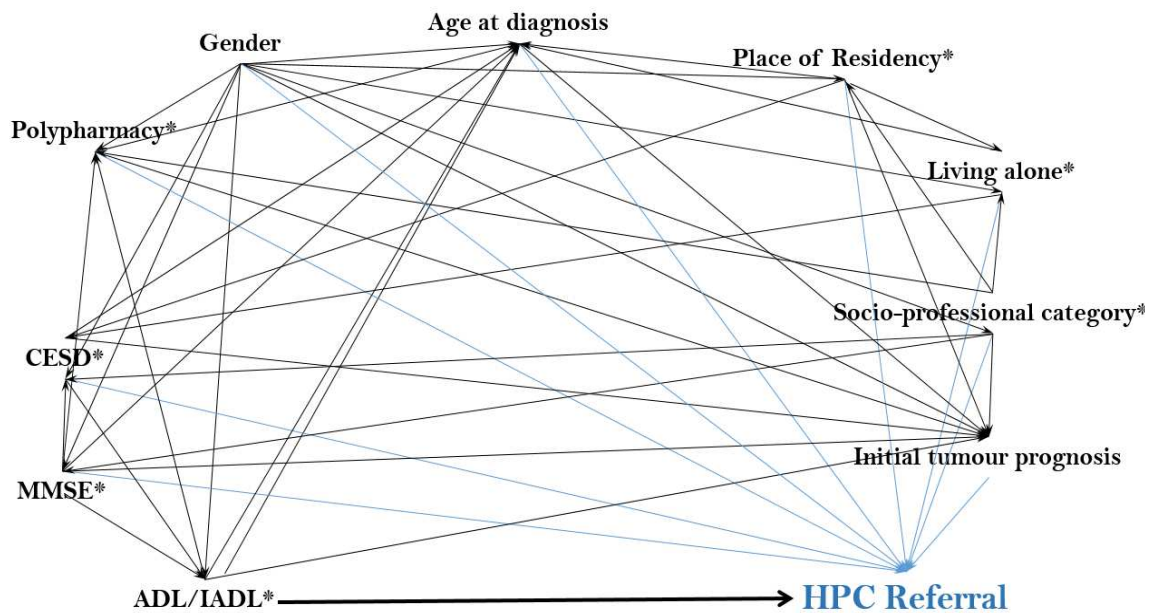
CESD = Centre for epidemiologic studies depression scale

SCP = Socio-professional category



* = Variables collected during cohort follow-up, before cancer diagnosis

Figure S1. Relationship analysis for the effect of nutritional state on survival. Directed Acyclic Graph.



* = Variables collected during cohort follow-up, before cancer diagnosis

Figure S2. Relationship analysis for the effect of neurologic state on survival. Directed Acyclic Graph.

Supplementary references

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