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Influence of sex on the incidence of colorectal cancer: considering the influence of gender mechanisms

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ABSTRACT

Context: Differences in colorectal cancer (CRC) incidence between men and women are documented, but the role of gender mechanisms in explaining these disparities remains underexplored. CRC, the third deadliest cancer worldwide, is often analyzed through "biological" sex differences, without a clear distinction between innate and socially acquired factors. Gender mechanisms, including social roles, behaviors, and access to healthcare, may significantly influence CRC risk.
Objective: This study quantifies the proportion of the effect of gender mechanisms on the relationship between sex assigned at birth and CRC incidence, adopting a social epidemiology approach.
Method: Using data from the CONSTANCES cohort and the French National Health Insurance database (SNDS), we identified relevant covariates with a Directed Acyclic Graph (DAG). Mediation analyses estimated the contribution of socioeconomic, behavioral, anthropometric and medical factors as gender-related mechanisms.
Results: Men have a higher risk of CRC compared to women (OR: 1.54 [1.33; 1.79]). Men exhibit lower cultural capital, higher social and economic capital, more frequent risk behaviors, and higher BMI. Gender mechanisms account for 30 % of the association between sex assigned at birth and CRC incidence, in the imputed data, and up to 50 % in the complete cases. Among the gender mechanisms, BMI emerged as the main mediator.
Conclusion: This study reveals that gender-based health inequalities in CRC incidence are partially explained by differences in exposure to social and behavioral risk factors. These findings underscore the importance of integrating gender dynamics into public health strategies for CRC prevention and intervention, focusing on addressing gender-based risk factor exposure.

1. Introduction

Although men and women present distinct biological characteristics, significant differences in disease prevalence cannot be solely explained by sexual dimorphism (Krieger, 2003). These disparities result from differentiated physical, social, and cultural exposures based on the sex category defined at birth, shaped gender normative systems, influencing both health behaviors and biological responses. This interaction between biology and social context reflects what is often termed *acquired biology or embodiment*—the concept that social environment and gendered experiences can modify biological traits throughout life (Kelly-Irving and Delpierre, 2021).

While sex refers to innate biological characteristics (such as chromosomes and reproductive organs), gender encompasses the social norms, roles and behaviors assigned to individuals based on their sex, which can in turn shape biological outcomes (Hammarström et al., 2014). For instance, health-related behaviors - such as diet, physical activity, and stress management-are influenced by gendered social

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expectations, ultimately impacting biological markers like metabolic health (Strack et al., 2022). Building on the entanglement concept proposed by Springer et al. (2012), we adopt a perspective in which the biological and social dimensions of sex and gender are understood as interdependent and mutually shaping across the life course. This framework allows us to consider sex not as a fixed biological given, but as embedded in social structures and experiences that contribute to differential health exposures. Colineaux et al. define gender mechanisms as "the sociocultural and institutional structures, processes, and practices that influence and maintain differentiated roles, behaviors, and expectations between sexes in a society" (Colineaux et al., 2023).

Although both sex and gender mechanisms likely contribute to health differences between men and women, few epidemiological studies integrate both dimensions in their analyses (Doyal, 2001; Gahagan et al., 2015; Ginsburg et al., 2023). Some diseases, such as ovarian or prostate cancers, are directly linked to sexual dimorphism (Bray et al., 2024). However, for most diseases, including colorectal cancer (CRC), disparities result from complex interactions between innate biological and gender mechanisms. CRC is one of the most common and deadly cancers worldwide (Bray et al., 2024). In France, the categories 'male' and 'female' refer to the legal system of binary categorization of sex assigned at birth on the basis of the observed genital phenotype, CRC is the third most frequent cancer in men (26 212 cases in 2023) and the second in women (21 370 cases) (Lapôtre-Ledoux et al., 2023). In French epidemiological studies, sex is often used without explicitly specifying whether it serves as a proxy for gender, even though social and cultural factors contribute to health disparities between men and women (Martinez et al., 2024).

France has a universal health system covering almost the entire population mainly financed by public health insurance, therefore free for individuals. Cancer screening programs are organized for the whole population for cervical, breast and colorectal cancer. Physicians can also prescribe screening on an individual basis to their patients. Regarding CRC, free screening is offered every two years to people aged 50 to 74. Despite a decrease in incidence since 1995 for rectal cancer in men and since 2005 for colon cancer disparities persist, with men showing higher incidence rates despite lower screening participation (Ahmed et al., 2023; Pornet et al., 2010; SPF, n.d.; Synthèse - Estimations Nationales de l'incidence et de La Mortalité Par Cancer En France Métropolitaine Entre, 1990 et 2018 - Ref: SYNINCNAT2019, n.d.). Some studies attribute these disparities to sexual dimorphism, due to hormonal differences between sexes (McMichael and Potter, 1980; Newcomb et al., 2007; Rossouw et al., 2002), while others emphasize the role of gender-related sociocultural factors and behaviors, such as smoking, alcohol consumption, diet, and overweight (Jacobs et al., 2007; Richardson et al., 2016). However, very few studies analyze the influence of both sex and gender on CRC incidence (Martinez et al., 2024).

Individuals assigned male or female at birth experience distinct life trajectories, influenced by roles shaped by their sex at birth, which can modify their biological functioning over time. (Heise et al., 2019; Mauvais-Jarvis et al., 2020). These systemic gender mechanisms vary across social groups and contexts, reinforcing health inequalities (Heise et al., 2019).

Analyzing CRC incidence through a gender- and sex-sensitive lens is thus necessary to fully understand the mechanisms driving these inequalities. This approach acknowledges that biology is not solely innate but is also shaped by lived experiences and social conditions.

The main objective of this study is to evaluate the proportion of the effect of gender mechanisms on the relationship between sex at birth and CRC incidence. Specifically, we aim to determine the mediating role of these mechanisms by evaluating the association between sex at birth and the sociocultural structures and risky behaviors in a French national cohort.

2. Materials and methods

2.1. Data and population

The French CONSTANCES population-based cohort enrolled volunteers randomly from 2012 to 2021, aged 18–69 years at inclusion. Participants were recruited through 21 health-screening centres (HSCs) located in 20 departments in the principal regions of France, with the Lille HSC also welcoming individuals from the Pas-de-Calais department (Henny et al., 2020). These volunteers were included in the French general health insurance system that covers 85 % of the adult population in France, and excluded self-employers, farmers and undocumented immigrants. Participants completed annual self-administered questionnaires on their lifestyle, health, social, and personal characteristics (Zins et al., 2015). Additionally, they underwent physical examination in the HSCs. The response rate at enrollment in the CONSTANCES cohort was of 7.3 % (Goldberg et al., 2017), in line with other international cohorts (e.g., 5.5 % for the UK Biobank) (Toledano et al., 2015). All the procedures are detailed at www.constances.fr.

Participants' data were matched to the French compulsory national Health Insurance database (SNDS), which includes information on all reimbursed medications, hospitalizations, and long-term illness care (Bezin et al., 2017), for a period from January 1, 2007 to December 31, 2021. These data do not include clinical results but only diagnosis associated with the medical acts and hospital stay invoiced to health insurance.

The Validation Diagnostic Platform (VDP) included a randomly selected group of participants to validate health events such as cancer. Participants with self-reported cancer diagnoses or cancer codes in their medical records (SNDS) were contacted by investigators via telephone to verify their information. Investigations were deemed complete if the participant was reached, or incomplete if they could not be contacted. Cancer cases were classified as "confirmed" if verified or "not confirmed" if verification was not possible. The process concluded when sufficient information was collected, with outcomes including completion, errors, abandonment, refusal, or death.

A second step was initiated if the cancer case was confirmed. The information was sent to two cancer registry experts to obtain additional details on the cancer's location and circumstances via medical records. This "adjudication step" involved validation of cancer cases with coding or recoding of tumors according to the International Classification of Diseases, Tenth Edition (ICD-10). Once the coding was completed, the adjudication process was considered finished. Incomplete adjudications could not validate the cancer diagnosis due to benign tumors, metastases, or recurrences. The adjudication process was conducted from 2013 to 2019, with the last available follow-up in 2019.

2.2. Measures

2.2.1. Approach and conceptual framework

In this study, we selected our covariates using an approach based on scientific literature and the conceptual framework provided by our Directed Acyclic Graph (DAG) (Fig. 1). The DAG helped map the cause-and-effect relationships between sex assigned at birth, gender mechanisms, and CRC incidence, identifying relevant pathways and potential confounders (Colineaux et al., 2022a,b). This tool ensured our variable selection was grounded in both theoretical and empirical evidence, offering a structured approach to understanding risk factor interactions within our population.

2.2.2. Main outcome: incident CRC cases between 2013 and 2021 (Fig. 2 and supplementary Figure 1)

A total of 205 203 volunteers were enrolled in CONSTANCES between January 2012 and May 2021. After excluding 589 individuals with a personal history of colorectal cancer (CRC), our baseline sample consisted of 204 614 individuals. We included incident CRC cases

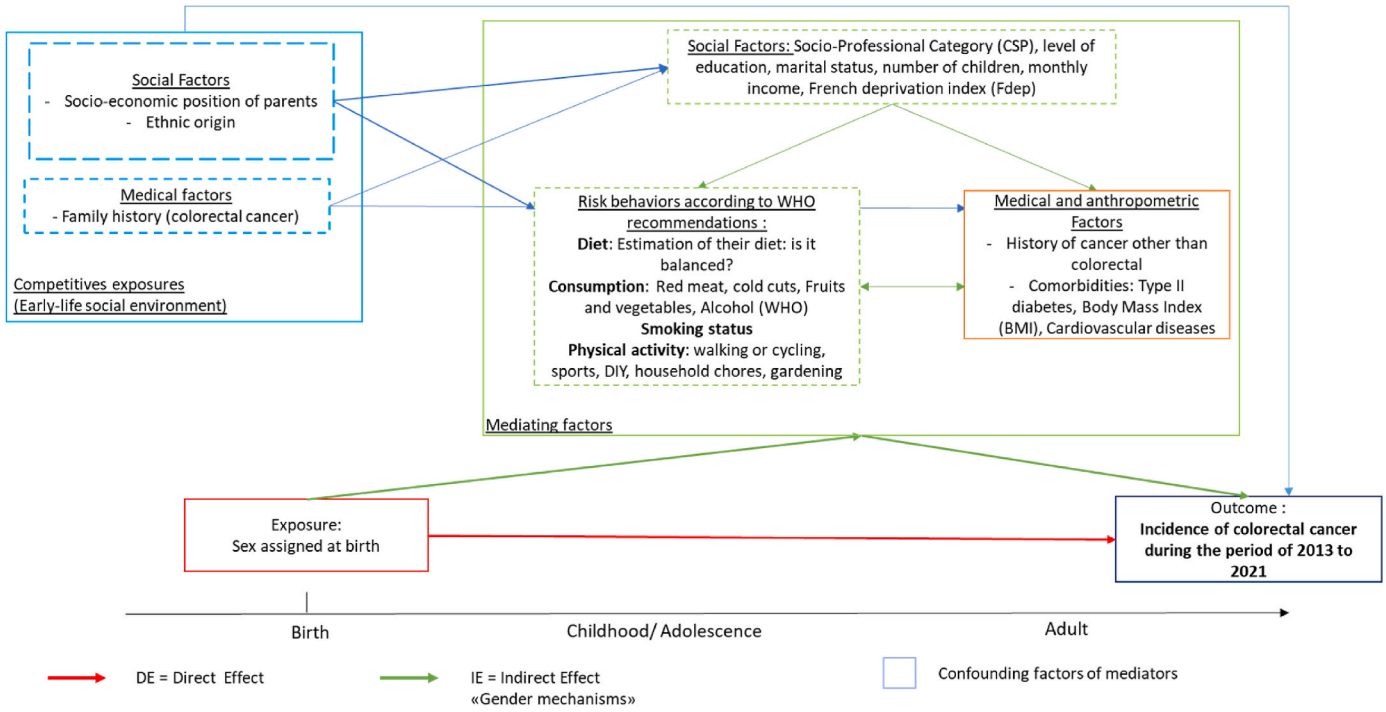


Fig. 1. The Directed Acyclic Graph (DAG) of this study.

identified through annual self-reported questionnaires, SNDS records, or both from 2013 to 2021. Participants reported any CRC diagnosis in the past 12 months, with 2020 as the last follow-up. The SNDS databases analyze pathologies and associated healthcare expenses. Using the SNDS database mapping tool (pathology and hospitalization algorithm), we identified CRC cases based on ICD-10 codes for malignant tumors or carcinoma in situ of the colon, rectosigmoid junction, or rectum (C18-C21 and D01.0-D01.2). This process identified 934 cases, but 31 had a previous CRC history identified in the VDP, leaving 903 cases, classified into two groups: self-reported only (N = 133) and identified in the SNDS records (N = 770).

Among the 770 CRC cases initially identified in the SNDS records, we excluded 15 that were not confirmed after investigation by the CONSTANCES investigators and 13 whose coding was revised during the adjudication step by cancer registry experts, no longer correspond to CRC. This resulted in a total of 742 incident CRC cases. Of these, 121 were confirmed and validated by cancer registry experts during the adjudication process, while the remaining 621 were identified through SNDS records but were not further investigated by the CONSTANCES investigators.

Among the 133 self-reported cases, we excluded 56 not investigated by phone, 20 contacted by phone but whose study was abandoned due to reasons such as refusal or dropout, 25 whose diagnosis could not be confirmed, and 29 without ICD-10 codes for CRC (C18-C21 and D01.0-D01.2) following the adjudication step by cancer registry experts. As a result, only 3 self-reported CRC cases were included in the final population of incident CRC cases.

Our final study population is 204 172, consisting of 745 incident CRC cases and 203 427 individuals without CRC over the period of 2013–2021 (Fig. 1 and Supplementary Fig. 1).

2.2.3. Main exposure: sex at birth

In our study, the sex recorded on civil status documents and registered in the SNDS at the time of participant selection (social security number: 1: male; 2: female) was available. The 'sex' variable in CONSTANCES refers to the legal system of binary sex categorization (female/male), assigned at birth based on observed genital phenotype (female for individuals with a vulva; male for individuals with a penis). Therefore, in our study, the terms 'woman' and 'man' refer to individuals assigned female or male (coded as 1) at birth, according to this legal binary system.

2.2.4. Covariates

This study, we used the concept of **gender mechanisms**, defining gender as the effect of sex category on socio-behavioral or medical characteristics within a society. Using the data from the CONSTANCES cohort, we created a **DAG**, classifying covariates as confounders, mediators, or competitive exposures. By modeling the direction and sequence of these factors, we systematically identified variables that might distort the associations of interest. This ensured our analyses accurately reflected the interplay between sex, gender mechanisms, and CRC incidence (Fig. 1).

2.2.5. Confounding factor

Age was categorized (<50, 50–60, and 60–75 years) because its relationship with colorectal cancer (CRC) incidence was not linear.

2.2.6. Competitive exposure: early-life environment

In relation to the effect of sex on CRC incidence, participants' early-life social environment was considered a competitive exposure. These competitive exposures could modify the effect of gender mechanisms on the outcome. Two social factors—parents' occupational classification (POC) and parents' ethno-racial background—and one medical factor—family history of CRC—made up the early-life social environment in our study (Fig. 1).

The occupational classification in France classify occupations based on criteria like occupation, status, and sector. We grouped POC during participants' adolescence into advantaged (POC advantaged: executives and higher intellectual and intermediate professions) and disadvantaged (POC disadvantaged: farmers, artisans, employees, workers, homemakers, the unemployed, and others). These groupings are based on the economic and psychosocial conditions of jobs, which can significantly impact workers' health. (Nomenclatures Des Professions et Catégories Socioprofessionnelles Des Emplois Salariés Des Employeurs Privés et

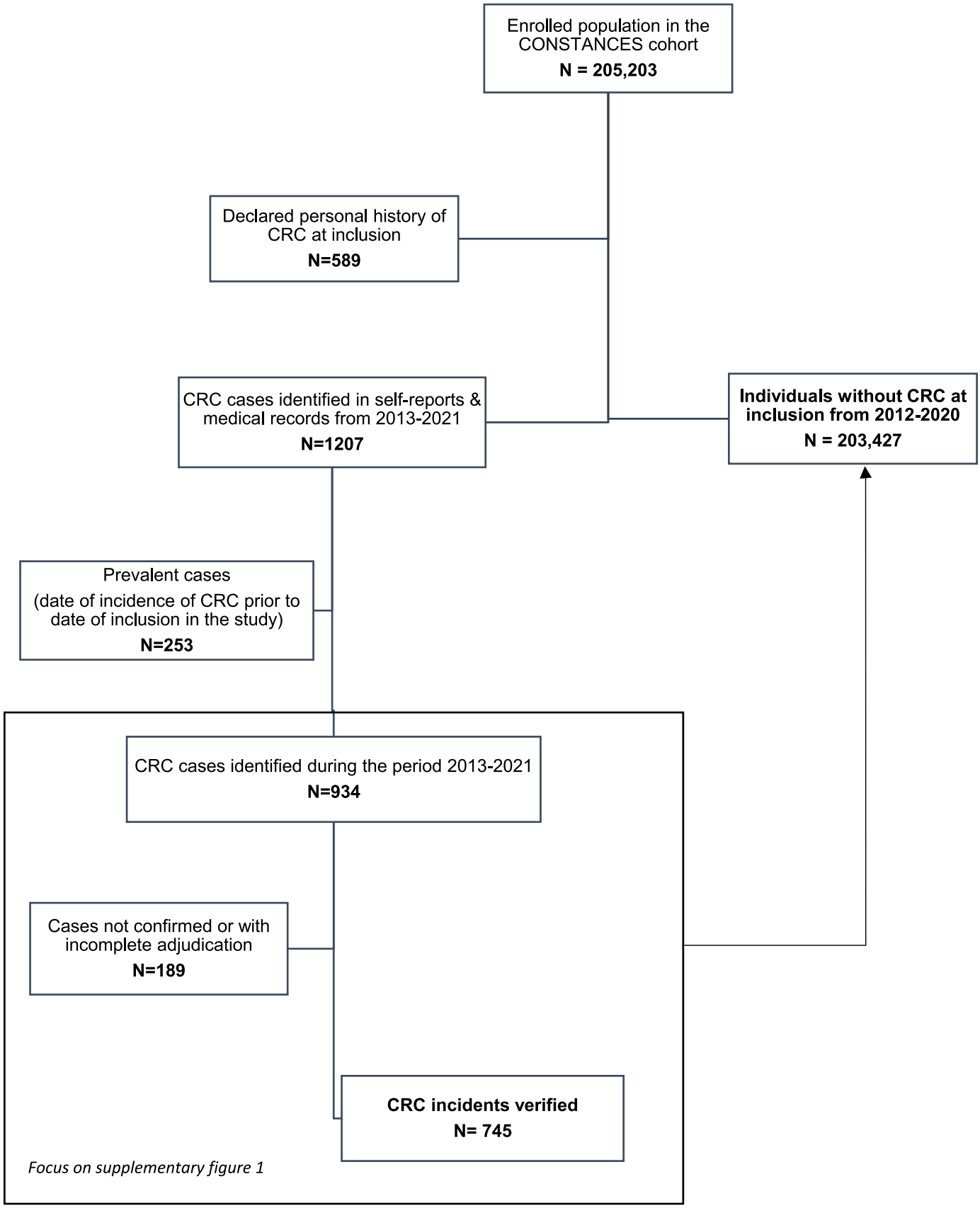
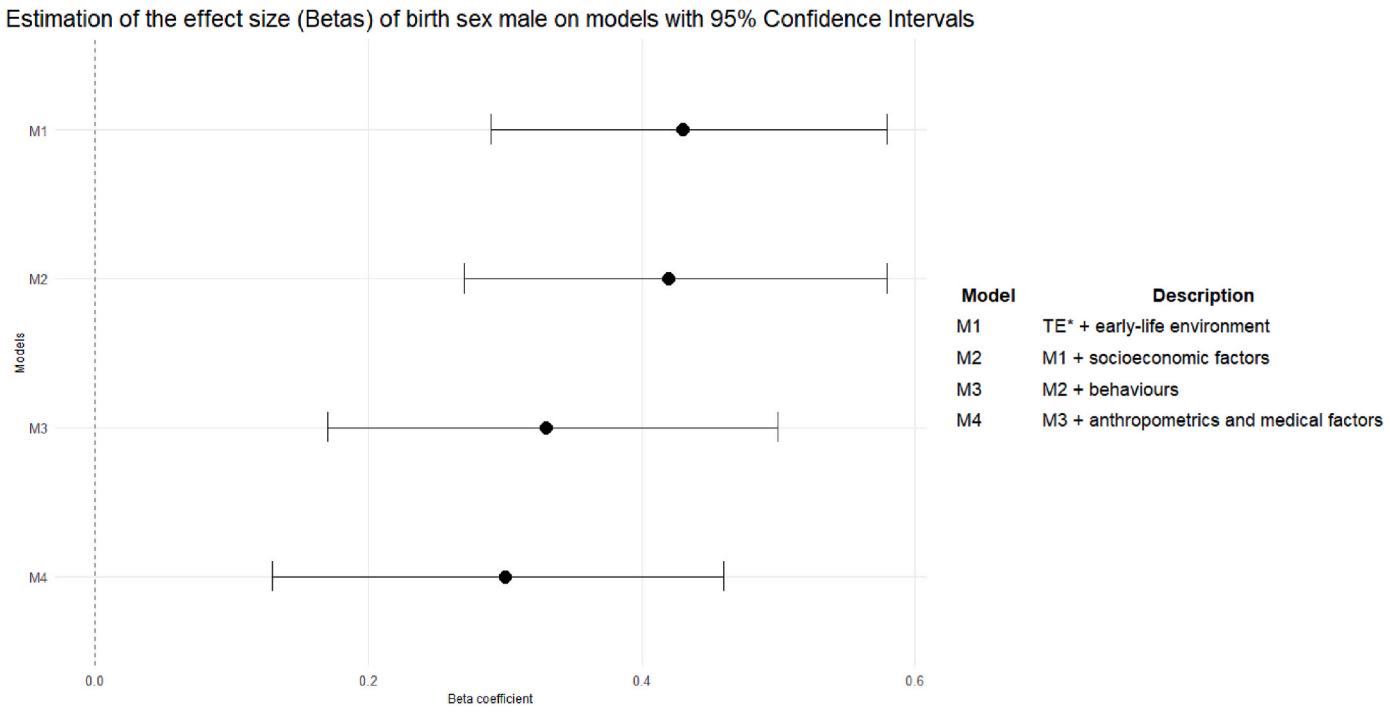


Fig. 2. The flow chart of this study.



	Model 1		Model 2		Model 3		Model 4	
	β[1] (95% CI)[2]	OR (95% CI)	β (95% CI)	OR(95% CI)	β (95% CI)	OR(95% CI)	β (95% CI)	OR(95% CI)
Women (Reference)	—	—	—	—	—	—	—	—
Men	0.43 (0.29, 0.58)	1.54 (1.33, 1.78)	0.42 (0.27, 0.57)	1.53 (1.31, 1.77)	0.33 (0.17, 0.49)	1.39 (1.19, 1.64)	0.30 (0.13, 0.46)	1.34 (1.14, 1.58)

[1]**β**= Log Relative Risk, [2] **CI** = Confidence Interval

Model 1 (M1) : TE on CRC Incidence adjusting only for competitive exposures (parents' Socio-Professional Categories, parents' ethno-racial background and family history of colorectal cancer) and age at inclusion*
*Model 2 (M2) : CDE** on CRC Incidence adjusting on M1 and block 1 ; social mediator factors (Socio-Professional Categories of individuals, French Social Deprivation Index, monthly net household income, level of education,* Partnership status *, number of children of the participant).*
*Model 3 (M3) : CDE** on CRC Incidence adjusting on M2 and block 2 ; behavior mediator factors (smoking, alcohol consumption, balanced diet, consumption of meat, cold cuts, vegetables, fruits, physical activity).*
*Model 4 (M4) : CDE** on CRC Incidence adjusting on M3 and block 3 ; medical and anthropometric mediator factors (personal history of cancer other than CRC, BMI, cardiovascular diseases, type II diabetes).*

**TE = Total Effect of birth sex male* **CDE = Controlled Direct Effect of Sex at Birth*

Fig. 3. Effect analysis describing the effects of sex on the incidence of colorectal cancer, using logistic regression (Odds Ratio (OR)) and log-binomial regression (beta coefficients (β)) with 95 % confidence intervals.

Publics | Insee, n.d.; Schreibauer et al., 2020; Torrès et al., 2022).

For parents' ethno-racial background, we used a proxy variable based on the geographical birth place and nationality of the parents and participants, following the methodology used in the second "Trajectoires et Origines" (TEO2) survey (Beauchemin et al., 2023) in France on migration. We defined "immigrant population" as first-generation immigrants (born abroad), second generation immigrants (born in France to at least one immigrant parent). Similarly, in the TEO2 survey, despite being French citizens, people from the overseas territories were included in the "immigrant population" category due to their socio-cultural and demographic experiences, which are often similar to those of immigrants (migration histories and socio-economic challenges distinct from the non-immigrant population). The "**non-immigrant population**" **includes** those born French with no immigrant background. Given the small sample sizes, we created a binary variable: non-immigrant vs immigrant.

The family history of CRC variable in the participants' parents was collected through the medical questionnaire.

2.2.7. *Mediating factors (Fig. 1)*

Based on the literature, we identified a priori 18 potential mediators (Heise et al., 2019; Mollborn et al., 2020; Weber et al., 2019). We considered gender mechanisms as a dynamic process, and thus we analyzed all the a priori factors available in CONSTANCES via the inclusion questionnaire that could modify the relationship between sex at birth and CRC incidence. We classified the mediating factors using

Bourdieu's concept of capital to address gender mechanisms through a systemic perspective on social processes and structures of inequality. This approach highlighted differences in access to resources (economic, social, and cultural capital) between men and women, allowing us to identify how gender inequalities operate as quantifiable mediating factors (BOURDIEU, 1979). Our DAG emphasises that gender mechanisms are not limited to direct causal relationships but are interconnected structural elements shaped by social dimensions. For example, the sex assigned at birth can influence the number of children a person has, which, in turn, impacts their social capital and influences health behaviours (e.g., family responsibilities are often managed by women (Melchior et al., 2007)). These interrelationships create a pathway through which social factors influence the occurrence of CRC. Consequently, based on their interdependence, we identified blocks of mediation according to their emergence in individuals' life trajectories.

2.2.8. Bloc 1: Sociocultural factors

- Occupational Classification (OC) of individuals (same classification as the parent's occupational classification: advantaged OC; reference: disadvantaged OC), as well as the monthly net household income (reference: less than 1500€). We also used the French Social Deprivation Index (Fdep) measured at the municipality level and used in quintiles (reference: Q1). These three variables were used to constitute the economic capital of participants.
- The level of education, defined by the highest diploma obtained, was used to reflect cultural capital (reference: primary degree).
- The social capital has been approached by using data on the number of children of the participants (reference: no children) as well as their marital status (reference: single). These gender role indicators are included as proxies of gendered life trajectories that may influence health behaviors and CRC risk.

2.2.9. Bloc 2: Behavioral

- The **risky health behaviors** associated with CRC risk were: smoking (smoker; ex-smoker (having consumed at least 100 cigarettes (5 packs), 50 cigarillos, 50 pipes, or 25 cigars in their lifetime); non-smoker); alcohol consumption defined by the World Health Organization ("no consumption"; "moderate consumption: $\leq$2 drinks per day for women and $\leq$3 drinks per day for men"; "non-recommended consumption: >2 drinks per day for women and >3 drinks per day for men"); self-reported balanced diet (yes; no); 4 diet variables (consumption of meat, cold cuts, vegetables, and fruits (once a week or less; 2 to 3 times a week; 4 times a week or more than once a day)); and physical activity outside of work, including walking or cycling, sports, DIY, household chores, and gardening (absent to low; moderate; high to very intense).

2.2.10. Bloc 3: Anthropometric and medical factors

- The participants' comorbidities included personal history of cancer other than CRC (yes; no); Body Mass Index (BMI: underweight and normal weight (<25 kg/m^2); overweight to obesity (>25 kg/m^2)); cardiovascular diseases (CVD), such as history of cardiovascular accident, hypertension, angina, lower limb arteritis (yes; no); and type II diabetes (yes; no), were assessed through self-reported questions. In addition to the influence of these co-morbidities on health behaviours, co-morbidities may influence contact with the healthcare system, which can influence the probability of diagnosing CRC (health surveillance effect).

2.3. Statistical analyses

The analyses were performed using STATA and RStudio 2023.12.1 + 402. Missing data for covariates, except for family history, were imputed using the multiple imputation by chained equations method with the MICE package (R, v3.10.0, R-Foundation for Statistical Computing, Vienne, Autriche), across 1,000 bootstrapped datasets. Data on family history were not imputed, as unreliable estimations could bias the analyses. No complementary variables on parents are available to guide accurate imputation, as the data are limited to the individual. Including such variables could introduce biases, as the family environment is not adequately captured. Therefore, missing values for this variable were grouped under "absence of information".

To strengthen the reliability and robustness of the final results obtained from multiple imputations, we compared them with those derived from complete cases (N = 90 279), that is, the sample in which no variable has missing data, except for the one concerning family history. We also created a random subsample from the database generated by multiple imputation, matching the size of the complete cases sample, to compare the distributions between the two samples (N = 90 279). Finally, we also compared the final results obtained from multiple imputations to those obtained without multiple imputations, where missing cases were grouped into a missing category.

2.3.1. Descriptive analyses

We described both sexes based on the socio-demographic variables and the a priori identified mediators, including missing data, sample sizes, and percentages by category. Pearson's chi-squared test or Fisher's exact test were also calculated. It provides a general snapshot of differences between men and women in the cohort prior to further data processing (Table 1). We then analyzed the relationship between covariates and CRC risk using the imputed dataset. Table 2 presents the characteristics of individuals with and without CRC during the study period (2013–2021). This table highlights key socio-demographic, behavioral, and medical and anthropometric differences between these groups, offering insights into potential associations.

2.3.2. Mediation analyses: Effect attenuation analyses

For the effect analyses, we applied methods developed by Vander Weele and Pearl (Pearl, 2012; VanderWeele, 2016). Relying on our DAG, we tested the assumption of no residual confounding for the relationships between the exposure and mediators, the exposure and the outcome, and the mediators and the outcome. As sex precedes the blocks of mediators, which in turn precede the incidence of CRC, we considered this temporal ordering in the analyses. Using logistic regression models, we obtain the odds ratios (OR) and estimate both the direct and indirect effects of sex on colorectal cancer incidence using log-binomial regression, obtaining the beta coefficients (Colineaux et al., 2022a,b; VanderWeele, 2016).

2.3.3. Total effect of sex: Overall Effect of Sex at birth on CRC incidence

The total effect (TE) of sex encompasses all pathways linking sex attributed to birth to CRC incidence, highlighting differences in CRC distribution between males and females, as well as their early-life environment. Model 1 estimates this effect by analyzing CRC incidence according to the sex category, adjusted for age at inclusion and competitive exposures, with the TE estimated by the sex coefficient (or OR) in the model.

2.3.4. Controlled direct effect of sex: effect of sex at birth not mediated by the blocks of mediators

The controlled direct effect (CDE) of sex represents the remaining effect on colorectal cancer (CRC) incidence after controlling for mediator blocks. We used three models to integrate the mediators one by one and decomposed them by adding factors sequentially (Annex 1). The remaining direct effect is captured by the sex coefficient in the model, which we interpret as the effect of sex not explained by the mediators.

Table 1
Principal characteristics of the population of this study by sex (N = 204 172).

Variables		Population	Men (N = 94 475)	Women (N = 109 697)	Pvalue*
Outcome					
Incident of colorectal cancer between 2013 and 2021	Yes	745 (0.4 %)	432 (0.5 %)	313 (0.3 %)	<0.001
	No	203 427 (99.6 %)	94 043 (99.5 %)	109 384 (99.7 %)	
Confounding factors					
Age group at inclusion	<50 years old	114 506 (56.1 %)	51 841 (54.9 %)	62 665 (57.1 %)	<0.001
	50–60 years old	43 685 (21.4 %)	20 292 (21.5 %)	23 393 (21.3 %)	
	60–75 years old	45 981 (22.5 %)	22 342 (23.6 %)	23 639 (21.6 %)	
Competitive exposure: early-life enrironment					
Ethno-racial origin	Majority population	177 380 (86.9 %)	82 316 (87.1 %)	95 064 (86.7 %)	<0.001
	Other groups	23 518 (11.5 %)	10 737 (11.4 %)	12 781 (11.6 %)	
	Missing	3274 (1.6 %)	1422 (1.5 %)	1852 (1.7 %)	
Parents' Occupation Classification (POC)	Disadvantaged POC	114 137 (55.9 %)	53 114 (56.2 %)	61 023 (55.6 %)	<0.001
	Advantaged POC	83 706 (41.0 %)	38 600 (40.9 %)	45 106 (41.1 %)	
	Missing	6329 (3.1 %)	2761 (2.9 %)	3568 (3.3 %)	
Family history	CRC	8372 (4.1 %)	3951 (4.2 %)	4421 (4.0 %)	<0.001
	Cancer other than CRC	60 691 (29.7 %)	27 427 (29.0 %)	33 264 (30.3 %)	
	Absence of information	135 109 (66.2 %)	63 097 (66.8 %)	72 012 (65.7 %)	
Social factors					
Partnership status	Single	55 659 (27.3 %)	25 284 (26.7 %)	30 376 (27.7 %)	<0.001
	Married or civil partnership	119 193 (58.4 %)	57 656 (61.0 %)	61 537 (56.1 %)	
	Separated, divorced, or widowed	25 160 (12.3 %)	9434 (10.0 %)	15 726 (14.3 %)	
	Missing	4160 (2.0 %)	2102 (2.2 %)	2058 (1.9 %)	
Number of children	Missing	13 235 (6.5 %)	6216 (6.6 %)	7019 (6.4 %)	<0.001
	No children	74 433 (36.5 %)	38 691 (41.0 %)	35 742 (32.6 %)	
	1 child	27 577 (13.5 %)	11 773 (12.5 %)	15 804 (14.4 %)	
	2 children	57 326 (30.0 %)	24 222 (25.6 %)	33 104 (30.2 %)	
	3 children or more	31 601 (16.6 %)	13 573 (14.3 %)	18 028 (16.4 %)	
Economic factors					
Occupation Classification (OC)	Disadvantaged OC	79 608 (39.0 %)	33 293 (35.2 %)	46 315 (42.2 %)	<0.001
	Advantaged OC	112 021 (54.9 %)	55 353 (58.6 %)	56 668 (51.7 %)	
	Missing	12 543 (6.1 %)	5829 (6.2 %)	6714 (6.1 %)	
Net monthly household income	Less than 1500€	21 554 (10.6 %)	9091 (9.6 %)	12 463 (11.4 %)	<0.001
	From 1500€ to 2100€	21 968 (10.8 %)	9143 (9.7 %)	12 825 (11.7 %)	
	From 2100€ to 2800€	29 707 (14.5 %)	13 215 (14.0 %)	16 492 (15.0 %)	
	From 2800€ to 4200€	59 719 (29.2 %)	28 250 (29.9 %)	31 469 (28.7 %)	
	4200€ or more	55 321 (27.1 %)	28 293 (29.9 %)	27 028 (24.6 %)	
	Missing	15 903 (7.8 %)	6483 (6.9 %)	9420 (8.6 %)	
The French social deprivation index (Fdep)	Q1: Very low	40 893 (20.0 %)	19 191 (20.3 %)	21 702 (19.8 %)	<0.001
	Q2: Low	40 791 (20.0 %)	18 902 (20.0 %)	21 889 (20.0 %)	
	Q3: Average	40 859 (20.0 %)	18 888 (20.0 %)	21 971 (20.0 %)	
	Q4: High	40 817 (20.0 %)	18 527 (19.6 %)	22 290 (20.3 %)	
	Q5: Very high	40 812 (20.0 %)	18 967 (20.1 %)	21 845 (19.9 %)	
Cultural factor					

(continued on next page)

Table 1 (*continued*)

Variables		Population	Men (N = 94 475)	Women (N = 109 697)	Pvalue*
Level of education	No diploma or primary degree	16 980 (8.3 %)	7792 (8.2 %)	9188 (8.4 %)	<0.001
	Technical degree	32 060 (15.7 %)	18 081 (19.1 %)	13 979 (12.7 %)	
	Secondary degree	33 046 (16.2 %)	14 543 (15.4 %)	18 503 (16.9 %)	
	University degree: 2 or 3 years	52 520 (25.6 %)	20 654 (21.9 %)	31 666 (28.9 %)	
	University degree: master's degree or more	65 787 (32.2 %)	31 463 (33.3 %)	34 324 (31.3 %)	
	Missing	3979 (2.0 %)	1942 (2.1 %)	2037 (1.8 %)	
Behaviors					
Balanced diet	Yes	154 040 (75.4 %)	70 860 (75.0 %)	83 180 (75.8 %)	<0.001
	No	33 282 (16.3 %)	16 039 (17.0 %)	17 243 (15.7 %)	
	Missing	16 850 (8.3 %)	7576 (8.0 %)	9274 (8.5 %)	
Alcohol	No consumption	28 661 (14.0 %)	9602 (10.2 %)	19 059 (17.4 %)	<0.001
	Moderate cosumption	131 817 (64.6 %)	64 313 (68.1 %)	67 504 (61.5 %)	
	Non-recommended consumption	18 702 (9.2 %)	10 999 (11.6 %)	7703 (7.0 %)	
	Missing	24 992 (12.2 %)	9561 (10.1 %)	15 431 (14.1 %)	
Smoking status	No smoker	93 627 (45.9 %)	38 532 (40.8 %)	55 095 (50.2 %)	<0.001
	Smoker	36 164 (17.7 %)	17 834 (18.9 %)	18 330 (16.7 %)	
	Ex-smoker	65 989 (32.3 %)	34 263 (36.3 %)	31 726 (28.9 %)	
	Missing	8392 (4.1 %)	3846 (4.1 %)	4546 (4.2 %)	
Physical activity	Absent to low	54 001 (26.5 %)	26 235 (27.8 %)	27 766 (25.3 %)	<0.001
	Moderate	42 230 (20.7 %)	19 275 (20.4 %)	22 955 (20.9 %)	
	High to very intense	100 688 (49.3 %)	46 118 (48.8 %)	54 570 (49.8 %)	
	Missing	7253 (3.5 %)	2847 (3.0 %)	4406 (4.0 %)	
Personal anthropometric and medical factors					
Type II diabetes	Yes	5339 (2.6 %)	3773 (4.0 %)	1566 (1.4 %)	<0.001
	No	194 933 (95.5 %)	88 865 (94.1 %)	106 068 (96.7 %)	
	Missing	3900 (1.9 %)	1837 (1.9 %)	2063 (1.9 %)	
Personal history of cancer other than CRC	Yes	9376 (4.6 %)	3322 (3.5 %)	6054 (5.5 %)	<0.001
	No	187 171 (92.0 %)	87 662 (93.2 %)	99 509 (91.0 %)	
	Missing	6880 (3.4 %)	3059 (3.3 %)	3821 (3.5 %)	
BMI	Underweight and normal weight	114 032 (55.8 %)	45 265 (47.9 %)	68 767 (62.7 %)	<0.001
	Overweight to obesity	85 884 (42.1 %)	47 166 (49.9 %)	38 718 (35.3 %)	
	Missing	4256 (2.1 %)	2044 (2.2 %)	2212 (2.0 %)	
Cardiovascular diseases	Yes	32 047 (15.7 %)	16 644 (17.6 %)	15 403 (14.0 %)	<0.001
	No	166 648 (81.6 %)	75 395 (79.8 %)	91 253 (83.2 %)	
	Missing	5477 (2.7 %)	2436 (2.6 %)	3041 (2.8 %)	

* P-value of chi-squared test.

2.3.5. *Indirect effect of sex: effect of sex at birth on CRC incidence that passes by the mediators*

The indirect effect (IE) of sex is the "eliminated" effect of sex at birth when controlling for mediator blocks. A decreasing IE as mediators are added highlights the impact of gender mechanisms on the sex/CRC relationship. It is calculated by subtracting the controlled direct effect from the total effect of sex. The 95 % confidence interval was obtained using 1,000 bootstrapped datasets. We selected women as the reference category, given their relatively lower CRC incidence compared to men. Thus, the IE represents the portion of the total effect of male sex mediated by environmental, medical, and social behavior factors. The proportion of the total effect (TE) "eliminated" through mediators is determined as follows:

$$IE\ (proportion\ of\ TE\ eliminated) = \left(\frac{TE - CDE}{TE}\right) \times 100$$

(where CDE represents the controlled direct effet)

Table 2
Characteristics of the populations with colorectal cancer (CRC) during the period from 2013 to 2021 and those without CRC during the same period (N = 204 172; sample from multiple imputation).

Variables		Population without CRC N = 203 427	Population with CRC N = 745	Pvalue*
Main exposure				
Sex at birth	Men	94 043 (46.2 %)	432 (58.0 %)	<0.001
	Women	109 384 (53.8 %)	313 (42.0 %)	
Confounding factor				
Age at inclusion	<50 years old	114 384 (56.2 %)	122 (16.4 %)	<0.001
	50–60 years old	43 460 (21.4 %)	225 (30.2 %)	
	60–75 years old	45 583 (22.4 %)	398 (53.4 %)	
Competitive exposure: early-life enrironment				
Ethno-racial origin	Majority population	179 553 (88.3 %)	651 (87.4 %)	0.456
	Other groups	23 874 (11.7 %)	94 (12.6 %)	
Parents' Occupation Classification (POC)	Disadvantaged POC	117 935 (58.0 %)	498 (66.9 %)	<0.001
	Advantaged POC	85 492 (42.0 %)	247 (33.1 %)	
Family history	CRC	8312 (4.1 %)	60 (8.0 %)	<0.001
	Cancer other than CRC	60 405 (29.7 %)	286 (38.4 %)	
	Absence of information	134 710 (66.2 %)	399 (53,6 %)	
Sociocultural factors				
Partnership status	Single	56 675 (27.9 %)	88 (11.8 %)	<0.001
	Married or civil partnership	121 071 (59.5 %)	510 (68.5 %)	
	Separated, divorced, or widowed	25 681 (12.6 %)	147 (19.7 %)	
Number of child	No children	78 616 (38.6 %)	237 (31.8 %)	<0.001
	1 child	29 468 (14.5 %)	95 (12.8 %)	
	2 children	61 358 (30.2 %)	254 (34.1 %)	
	3 children or more	33 985 (16.7 %)	159 (21.3 %)	
Fdep	Q1: Very low	40 743 (20.0 %)	150 (20.1 %)	0.924
	Q2: Low	40 643 (20.0 %)	149 (20 %)	
	Q3: Average	40 719 (20.0 %)	140 (18.8 %)	
	Q4: High	40 668 (20.0 %)	150 (20.1 %)	
	Q5: Very high	40 654 (20.0 %)	156 (20.9 %)	
Occupation Classification	Disadvantaged OC	86 324 (42.4 %)	286 (38.4 %)	0.026
	Advantaged OC	117 103 (57.6 %)	459 (61.6 %)	
Net monthly household income	Less than 1500€	24 355 (12.0 %)	79 (10.6 %)	0.214
	From 1500€ to 2100€	24 313 (12.0 %)	94 (12.6 %)	
	From 2100€ to 2800€	32 407 (15.9 %)	138 (18.5 %)	
	From 2800€ to 4200€	64 127 (31.5 %)	218 (29.3 %)	
	4200€ or more	58 225 (28.6 %)	216 (29.0 %)	
Level of education	Primary degree	17 921 (8.8 %)	114 (15.3 %)	<0.001
	Technical degree	32 691 (16.1 %)	172 (23.1 %)	
	Secondary degree	33 541 (16.5 %)	110 (14.8 %)	
	University degree: 2 or 3 years	52 973 (26.0 %)	175 (23.5 %)	
	University degree: master's degree or more	66 301 (32.6 %)	174 (23.4 %)	
Behavioral factors				
Balanced diet	Yes	167 509 (82.3 %)	623 (83.6 %)	0.360
	No	35 918 (17.7 %)	122 (16.4 %)	
Consumption of meat	Once a week or less	75 341 (37.0 %)	270 (36.3 %)	0.582
	2 to 3 times a week	77 945 (38.3 %)	299 (40.1 %)	
	4 times a week or more than once a day	50 141 (24.7 %)	177 (23.6 %)	
Vegetables	Once a week or less	30 499 (15.0 %)	101 (13.7 %)	0.528
	2 to 3 times a week	108 390 (53.3 %)	407 (54.6 %)	
	4 times a week or more than once a day	64 538 (31.7 %)	237 (31.8 %)	
Fruits	Once a week or less	39 255 (19.3 %)	129 (17.3 %)	<0.001
	2 to 3 times a week	40 238 (19.8 %)	103 (13.8 %)	
	4 times a week or more than once a day	123 934 (60.9 %)	513 (68.9 %)	
Cold cuts	Once a week or less	145 659 (71.6 %)	516 (69.3 %)	0.162
	2 to 3 times a week	44 132 (21.7 %)	167 (22.4 %)	
	4 times a week or more than once a day	13 636 (6.7 %)	62 (8.3 %)	
Physical activity	Absent to low	55 702 (27.4 %)	192 (25.8 %)	0.001
	Moderate	43 477 (21.4 %)	123 (16.5 %)	
	High to intense	104 248 (51.2 %)	430 (57.7 %)	
Alcohol consumption	No consumption	34 114 (16.8 %)	98 (13.1 %)	<0.001
	Moderate cosumption	148 543 (73.0 %)	514 (69.0 %)	
	Non-recommended consumption	20 770 (10.2 %)	133 (17.9 %)	
Smoking status	No smoker	97 242 (47.8 %)	279 (37.4 %)	<0.001
	Smoker	37 656 (18.5 %)	108 (14.5 %)	
	Ex-smoker	68 529 (33.7 %)	358 (48.1 %)	
Personal anthropometric and medical factors				
Type II diabetes	Yes	5400 (2.7 %)	42 (5.6 %)	<0.001
	No	198 027 (97.3 %)	703 (94.4 %)	
Personal history of cancer other than CRC	Yes	9706 (4.8 %)	60 (8.1 %)	<0.001
	No	193 721 (95.2 %)	685 (91.9 %)	
BMI	Underweight and normal weight	116 180 (57.1 %)	297 (39.9 %)	<0.001
	Overweight to obesity	87 247 (42.9 %)	448 (60.1 %)	
Cardiovascular diseases	Yes	32 764 (16.1 %)	206 (27.7 %)	<0.001
	No	170 663 (83.9 %)	539 (72.3 %)	

* P-value of chi-squared test.

The reference categories for the mediators were established based on the absence of exposure to CRC risk factors, i.e., the most favorable environments and behaviors, as identified in the literature.

To verify our effect estimates and test hypotheses about complex relationships between our mediators, we conducted a sensitivity analysis using the 3-way Vander Weele method, which incorporates interactions between mediators. This method decomposes the total effect of sex by accounting for direct and indirect effects, as well as interactions among mediators. We modelled these interactions by including cross-term variables in the regression equations, allowing us to examine their impact on the sex/CRC relationship. We then tested the addition of these interactions in Model 4 by comparing the AIC and BIC of the model with and without interactions (Annex 2).

Finally, we compared all our results using log-binomial regression, which allows for direct estimation of relative risks and is particularly useful in studies with rare events, like colorectal cancer in our population.

3. Results

3.1. Description of the population

The study sample (n = 204 172) is described in Table 1. Women had higher cultural capital than men. However, women had less economic capital than men. They made up the majority of lower socioeconomic categories (disadvantaged OC), with nearly 40 % earning less than €2,800 per month. Their social capital was also lower in terms of marital status: women were more often divorced, separated, or widowed, and less often married or in civil partnerships. Health behavior differences were evident, as women had lower prevalence of smoking, alcohol consumption, and a sedentary lifestyle, while men were more likely to be overweight or obese, report an unbalanced diet, and have higher rates of cardiovascular diseases.

During the period from 2013 to 2021, 745 individuals had an incident CRC. The majority were aged between 60 and 75 at the time of inclusion. People with incident CRC had lower cultural capital compared to those without CRC, with the majority having an educational level equivalent to or lower than a high school diploma. Regarding economic capital, there was no statistically significant difference between the two groups. Individuals with incident CRC were, on average, more often divorced, separated, or widowed (Table 2). There was a significant difference between men and women in CRC cases, with 313 cases being women (42 %) and 432 being men (58 %). Over the eight-year period, this translates to an incidence rate of 35.8 cases per 100 000 person-years for women and 57.4 cases per 100 000 person-years for men. A risk analysis showing a significant difference in CRC risk between men and women (log-rank test $p < 0.001$) is provided in the supplementary figures (Supplementary Fig. 2). A detailed visualization of these differences over eight years is presented in the Kaplan-Meier curve (Supplementary Fig. 2).

3.2. Total and controlled direct effects of sex on CRC incidence

3.2.1. Total effect of sex on CRC incidence (Fig. 3)

Model 1 presents the total effect of sex on CRC incidence, while accounting for the early-life environment and age at inclusion. Men have a higher risk of developing CRC compared to women during the study period (β: 0.43 [0.29; 0.58]). Similarly, the logistic regression results showed that men have a 54 % higher risk (OR: 1.54 [1.33; 1.79] when compared to women.

3.2.2. Controlled direct effect of sex on CRC incidence (Fig. 3)

Model 2 represents the direct effect of sex on CRC incidence while controlling for social mediator factor (block 1). A stabilization of risk for men compared to women was found (β: 0.42 [0.27; 0.58], OR: 1.53 [1.32; 1.78]), suggesting that after adjusting for social factors, men still have a 53 % higher risk of CRC compared to women.

Model 3 represents the controlled direct effect (CDE) of sex, additionally controlled for block 2, which includes risk behaviors. A decrease in the CDE of sex was found (β: 0.33 [0.17; 0.50]/OR: 1.40 [1.19; 1.64]). Despite accounting for these behaviors, men still have a 40 % higher risk of CRC compared to women. A detailed analysis of the indirect effects of risk behaviors (block 2) on the total sex effect on CRC incidence is provided in Annex 1. This analysis shows that smoking status (β: 0.38 [0.22; 0.53], OR: 1.46 [1.25; 1.70]) and alcohol consumption (β: 0.38 [0.23; 0.54], OR: 1.47 [1.26; 1.71]) reduce the total sex effect on CRC incidence by 11 % ($IE = (\beta M1 - \beta M3) \div \beta M1 x 100$), IE = (0.43–0.38)÷ 0.38)).

Model 4 represents the direct effect of sex on CRC incidence, controlled for Block 3, which includes anthropometric and medical factors. The direct effect of sex, adjusted for all mediator blocks, decreases slightly (β: 0.30 [0.13; 0.46]/OR: 1.35 [1.14; 1.59]). This indicates that introducing all mediators reduces the total effect of sex by 30 % ((0.43–0.30)/0.43). The decomposition of Block 3 (Annex 1) highlights BMI as the most impactful factor (β: 0.29 [0.13; 0.46]/OR: 1.34 [1.14; 1.58]), reducing the sex effect by 32 %.

3.2.3. Sensitivity analysis

Interaction analyses yielded similar results, with Model 4 showing a Beta of 0.30 (95 % CI: [1.13; 1.46]). Furthermore, the AIC and BIC are worse, as they are higher, compared to the model without interactions. Therefore, in our context, the introduction of interactions is not relevant, as it neither improves the model fit nor enhances the interpretation of the relationships between gender mechanisms and the influence of sex at birth on CRC incidence (Annex 2).

Analyses were also conducted on the complete cases (N = 90 279) and demonstrated an influence of mediating factors on the relationship between sex at birth and CRC incidence (M1; Beta: 0.26 [0.00; 0.52] and M4; Beta: 0.13 [−0.16; 0.43]). However, despite a substantial reduction in the effect of sex at birth following the introduction of all mediator blocks, 50 % of the total effect is eliminated by gender mechanisms. This effect is non-significant and highlights a selection bias (Annex 3). Indeed, this complete case population, compared to a subsample of our imputed analysis dataset, was younger, more likely to have higher economic capital, and possessed greater cultural capital (Annex 4).

4. Discussion

4.1. Main results

Our study demonstrated the significant impact of gender mechanisms on the relationship between sex at birth and CRC incidence. Men were at higher risk of CRC than women (total effect for men: OR: 1.54 [1.33; 1.79], M1) and this disparity was partly explained by differences in social, behavioural, and anthropo-medical factors. Men had lower cultural capital, higher deleterious health risk behaviors (e.g., alcohol and tobacco consumption) and a higher BMI, despite having better economic and social capital. Adjusting for these factors accounted for 30 % of the total effect of sex on CRC risk in the imputed data and up to 50 % in the complete cases. The complete case population reflects a selected group of CONSTANCES participants, younger and more socially advantaged. These characteristics are associated with higher survey completion, introducing potential selection bias. However, even in this selected group, the influence of gender mechanisms on risk factor distribution and CRC incidence remained pronounced, underscoring their role across populations and life stages.

Our effect decomposition analyses highlighted the role of specific mediating factors, notably: smoking, alcohol consumption, and BMI. However, even after accounting for the identified mediators, a direct effect of sex on CRC risk remains, suggesting additional mechanisms not captured in our study.

4.2. Comparison with other studies

The analysis of mediating factors, particularly gender mechanisms, to explain the effect of sex assigned at birth on CRC incidence has been limited (Martinez et al., 2024). Sex assigned at birth reflects not only innate biological characteristics but also acquired biological effects and gender-related mechanisms. Most studies focus on biological differences, namely hormonal ones, without distinguishing between acquired and innate biological effects (Hang and Shen, 2021; Rodríguez-Santiago et al., 2024). Other research has centered on behavioral differences between men and women but has not fully incorporated explicit mediation analyses (White et al., 2018). Our findings align with research showing that risk behaviors, such as smoking, alcohol consumption, and BMI, play a role in sex differences in CRC incidence. These studies highlight the significant contribution of these factors to differences in CRC incidence between sexes (Brändstedt et al., 2012).

Our study showed that at least 30 % of the total effect of sex at birth on CRC incidence is mediated by gender mechanisms. The residual direct effect of sex, although attenuated, still suggests that part of the differences between men and women is not explained by the gender mechanisms identified. For instance, some studies have shown a protective effect of estrogens in women regarding the risk of CRC (McMichael and Potter, 1980; Newcomb et al., 2007; Rossouw et al., 2002) and suggested that testosterone may promote CRC (Hendifar et al., 2009; Sach and Whynes, 2009). However, this biological effect should not be interpreted as solely innate but also as potentially acquired over the life course. The concept of embodiment explains how the social, physical, and emotional environment shapes biology throughout life, considering the dynamic interaction between the environment and individual over time (Kelly-Irving and Delpierre, 2021). Thus, the residual effect of sex that we observe could result of a continuous adaptation of both men and women to their environments, reinforced by gendered experiences (Kelly-Irving and Delpierre, 2021; Krieger, 2003; S. Richardson and Shattuck-Heidorn, 2019). This suggests that the residual effect of sex may be linked to remaining uncaptured gender mechanisms and may pertain to an acquired biological effect.

Emerging research in oncology highlights the complex interaction between biological and socio-environmental factors in health outcomes, particularly regarding colorectal cancer (CRC). In the United States, disparities in CRC incidence between Black and White populations are increasingly attributed to structural mechanisms operating through intersectional categories such as race, gender, and socio-economic status (Brim et al., 2008; N, 2013; Wallace et al., 2011). These inequalities, exacerbated by the interactions between environmental and biological factors, affect exposure to health-related behaviors, access to healthcare, and other social determinants. Structural inequalities, including systemic racism and discriminatory policies, generate cumulative health disadvantages, as highlighted by Bailey et al. (2017). In our study, we aimed to incorporate a range of determinants likely to generate discrimination, including ethno-racial origin, lifelong socioeconomic status, and health-related behaviors. However, we could not include individuals' interactions with the healthcare system.

Healthcare access varies by gender and sex (Durand et al., 2021; Fon Sing et al., 2013) influencing health inequalities, especially in preventive behaviors and screening access (Chambers et al., 2020; Durand et al., 2021; Wray and Minaker, 2019). In France, CRC screening rates are lower in men (33.5 % versus 35.7 %), with regional disparities, particularly in the overseas departments (SPF, n.d.). The French healthcare system offers free screening for individuals aged 50–74, largely funded through the public health insurance system, but access can be hindered by logistical and cultural barriers. Regional disparities, particularly in remote areas, also reflect differences in healthcare infrastructure and availability of medical professionals. Additionally, gender-specific factors, such as societal norms and awareness campaigns, influence the uptake of screening, with men often being less engaged in preventive health measures. These findings suggest that socioeconomic and cultural factors may limit screening access. Our results support the idea that economic capital mediates the relationship between sex at birth and CRC incidence. International studies show that higher national income is linked to increased risk of CRC, particularly among individuals under 50 (Arnold et al., 2017; Bray et al., 2024; Vaccarella et al., 2022). The UK Office of National Statistics longitudinal study reveals that CRC incidence evolves with individual factors over time, with more pronounced disparities among women (Sturley et al., 2023). This study also showed that socio-economic differences in CRC incidence varied depending on the indicator used. Individual measures of socio-economic status based on education level and social class demonstrated associations similar to those found in our results. However, unlike our study and other UK studies, they did not find an association between disadvantaged areas and CRC incidence (Tweed et al., 2018). These findings highlight the need to consider gender mechanisms as a dynamic process influenced by society's social context. An unfavorable socioeconomic environment is often linked to higher-risk health behaviors (Joannès et al., 2022; Vaccarella et al., 2022). Our results highlight the impact of behavioral risk factors such as smoking, alcohol consumption, and BMI, which act as gender mechanisms influencing CRC incidence. Studies show higher rates of these risk factors in men, especially smoking and alcohol consumption (Botteri et al., 2023; de Vries et al., 2020; Richardson et al., 2016). A meta-analysis indicates that smoking combined with certain genetic polymorphisms may increase CRC risk (Raimondi et al., 2009), highlighting the interplay between biological and behavioral factors. In our study, BMI was the primary mediating factor, considered a gender mechanism due to both biological and acquired gender-related influences (Cooper et al., 2021; Obésité et surpoids, n.d.; Tchernof and Després, 2013). Men have a higher prevalence of overweight than women, both in our study and in France (Cara, 2023). This difference is partly due to sex hormones and gendered exposures like social norms affecting diet and physical activity (Hargrove, 2018; He et al., 2020).

4.3. Study limitations

4.3.1. Sex

In our study, the exposure 'sex at birth' is a binary variable (women/men), not accounting for the diversity of intersex and transgender individuals' experiences. These populations are underrepresented in research and require special attention regarding health and gender norms (Heise et al., 2019). Additionally, sex assigned at birth may not align with participants' gender identity in adulthood. While sex at birth is typically used as a proxy for legal sex, discrepancies can occur, especially among transgender individuals (approximately 1 % in France in 2023)(loict, 2023).

4.3.2. Gender mechanisms

We included a wide range of social, behavioral, and medical mediators, but it is likely that some gender mechanisms were not captured. Indeed, as previously mentioned, access to care varies according to the sex and gender of individuals (Durand et al., 2021; Fon Sing et al., 2013; Wray and Minaker, 2019). Higher screening participation rates among women, as well as a screening technique considered less effective at detecting anatomically challenging polyps in women, could also contribute to the higher incidence observed in men (White et al., 2018). The data available on CRC via the SNDS are limited and not exhaustive, covering only a small sample of cases. Furthermore, they do not distinguish between organized and individual screening, even though the mechanisms related to health inequalities may differ between these two approaches.

Additionally, we did not include mental health data, such as anxiety, depression, adversity or discrimination, which could influence CRC risk factors (C et al., 2023; Coldefy and Gandré, 2018). Indeed, in the SNDS, it would have been necessary to rely on antidepressant consumption to capture psychosocial risk, which complicates the development of an

exhaustive definition of these factors. Furthermore, in the CONSTANCES cohort, the available information was declarative and contained many missing data, which limited its precision.

These psychosocial factors can play a role in how individuals react to stress, social pressures, and gender norms throughout their lives (Karimi et al., 2019; O'Connor et al., 2021). Consequently, these unaccounted elements may explain some of the residual differences observed in CRC incidence between men and women. Furthermore, the factors considered as gender mechanisms in our study were measured through self-reported retrospective responses from participants. This leads us to hypothesize potential measurement errors that could underestimate the contribution of mediators, particularly concerning physical activity, diet, and personal and family history, the effects of which are evident despite their established involvement in CRC incidence (Cancer colorectal, n.d.). Moreover, alcohol consumption was measured using a WHO standardized definition, but the thresholds for consumption differ by sex. Despite the biological and clinical relevance of these sex-differentiated thresholds, we can hypothesize an attenuated effect of gender mechanisms, contributing to an underestimation of alcohol use in our population (International Guide for Monitoring Alcohol Consumption and Related Harm, n.d.; Lowik et al., 2024; S. Richardson and Shattuck-Heidorn, 2019).

In the context of our analysis, it is possible that the effects of different mediators may not always align in the same direction. Some factors may increase the risk of CRC, while others may reduce it (Mollborn et al., 2020). For example, high alcohol consumption often increases the risk, whereas behaviors like regular exercise may mitigate this risk (Keum and Giovannucci, 2019). Therefore, when interpreting the effects of mediators, it is possible that we may be underestimating the impact of gender mechanisms in our study.

We attempted to understand the directions of the mediation effects by conducting an interaction analysis. This analysis showed similar results across mediators, which could suggest that these mediators act in the same direction. However, even in such cases, it is still possible that not all mediators align in the same way, reflecting the complexity of the relationships between sex, gender mechanisms, and health outcomes (Heise et al., 2019). When mediators show divergent effects, this does not necessarily mean that gender mechanisms are underestimated. Rather, it may indicate the nuanced and multifaceted ways in which gender influences health, highlighting how certain factors interact and sometimes contradict each other. This complexity reflects the diverse ways in which gender-related behaviors impact health outcomes and underscores the need for a comprehensive interpretation of these relationships (Mollborn et al., 2020). In conclusion, even if some mediators have opposing effects, this does not undermine the importance of gender mechanisms. Rather, it suggests that these mechanisms are complex and that no single factor can fully explain the relationship between gender and CRC risk.

4.3.3. Selection bias in the CONSTANCES cohort

As do all cohort studies, the CONSTANCES database presents a potential selection bias. The voluntary participation in the epidemiological survey results in participants with relatively high cultural and economic capital, limiting the representativeness of the sample and making it difficult to extrapolate to the French population. It is possible that certain health inequalities related to gender and CRC are underestimated in our sample due to this bias. However, it is worth noting that the CRC incidence results in our study are close to the national estimates provided by the French cancer registry network FRANCIM, which reinforces the robustness of our findings despite this limitation. According to national cancer statistics, the incidence of CRC was higher in men than in women in France (54 % VS 46 % in 2018), with a sex ratio of 1.4 (Synthèse - Estimations Nationales de l'incidence et de La Mortalité Par Cancer En France Métropolitaine Entre, 1990 et 2018 - Ref: SYNINCNAT2019, n.d.). This difference between the sexes was also observed in our study, but with a slightly higher sex ratio.

4.3.4. Validation of cancer cases

Based on the SNDS database, among the 149 verified cases classified as "survey closed," only 121 were confirmed as incident CRC, representing 81 %. Applying this confirmation rate to the 621 "Not investigated" cases, we estimate that approximately 504 of them are actual incident CRC cases. However, as a national medico-administrative database, SNDS is recognized for its high-quality data, widely used in epidemiological studies (Bezin et al., 2017; Scailteux et al., 2019; Tuppin et al., 2017). Its inclusion of all reimbursed healthcare services in France strengthens disease identification accuracy and reduces the risk of misclassification.

Additionally, the structured validation process, involving cancer registry experts, ensures the reliability of the data in the randomly selected sample of cancer cases it received. By cross-referencing data sources and applying a rigorous case validation process, we have minimized potential biases, thus ensuring the robustness of our study population. Moreover, since the cases verified by registry experts come from a random sample, their characteristics should be similar on average, and any misclassification would introduce a conservative bias. Therefore, the effect of observed gender mechanisms is likely underestimated.

4.4. Study strengths

4.4.1. Methodological approach

Our framework combined logistic and log-binomial regressions to test the mediation of gender mechanisms, isolating both direct and indirect effects of sex on CRC incidence. By integrating blocks of mediators, we highlighted the roles of social factors, risk behaviors, and medical factors while respecting individuals' life trajectories.

Our approach to conceptualizing gender as a dynamic process influencing social factors, behaviors, and health outcomes is inspired by the intersectional theory developed by Crenshaw, which argues that health inequalities result from the interaction of multiple social, economic, and cultural factors (Colineaux et al., 2022a,b; Jackson and VanderWeele, 2019; Richman and Zucker, 2019). Within this framework, we applied a mediation method through gender mechanisms and interaction analysis, a method linked to intersectional theories and recent techniques developed in social epidemiology (Crenshaw, 1994; Jackson and VanderWeele, 2019; S. Richardson and Shattuck-Heidorn, 2019). This approach draws on quantitative applications, such as those of Bauer, although we did not directly use them in this study. Our results support the idea that health inequalities related to sex are structural and not solely due to biological differences.

4.4.2. Longitudinal perspective

We considered the evolution of social health inequalities throughout individuals' lives, adjusting for competitive exposures and mediation factors chronologically. Studies in oncology show that early environments influence adulthood health, and our approach applies this idea to CRC (Coley et al., 2021; Joannès et al., 2022).

5. Conclusion

Our study showed that gender mechanisms explained at least 30 % of the total effect of sex on CRC incidence. Few studies have explored gender mechanisms in relation to CRC from such a comprehensive perspective, combining mediation analysis with an understanding of biological, social, and behavioral interactions. These results pave the way for targeted strategies to prevent gender-related health disparities and call for greater integration of life contexts and structural inequalities in epidemiological analyses.

CRediT authorship contribution statement

Amalia Martinez: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data

curation, Conceptualization. **Nadine Hamieh:** Writing – review & editing, Methodology, Data curation. **Hélène Colineaux:** Writing – review & editing, Methodology. **Michelle Kelly-Irving:** Writing – review & editing, Resources, Project administration, Funding acquisition. **Pascale Grosclaude:** Writing – review & editing, Visualization, Validation, Methodology. **Emmanuel Wiernik:** Writing – review & editing, Methodology, Data curation. **Cyrille Delpierre:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sébastien Lamy:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Ethics approval statement

Ethics approval was not required for this study, as it relied exclusively on pre-existing, anonymized data from the CONSTANCES cohort and the French National Health Insurance Database (SNDS). All participants had previously provided informed consent at the time of inclusion in the CONSTANCES cohort. For more information on the CONSTANCES cohort's ethical approvals and procedures, please refer to: www.constances.fr.

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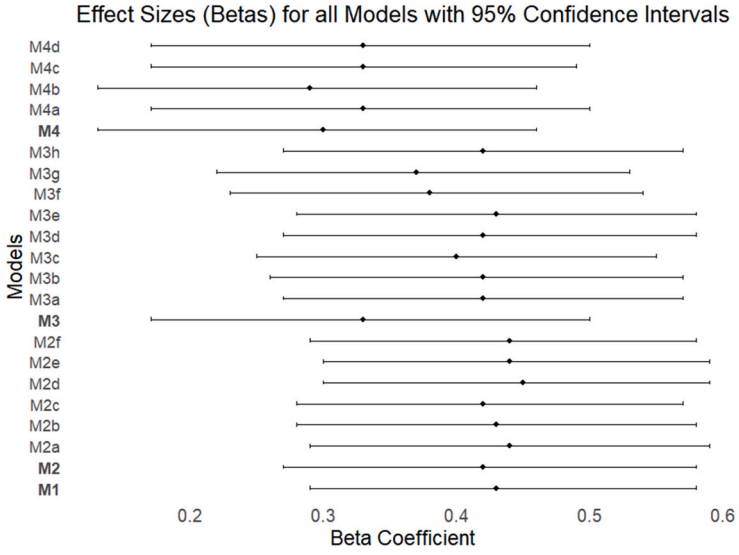
None of these funding sources had any role in the design of the study, collection and analysis of data or decision to publish.

Declaration of competing interest

The authors declare they have nothing to disclose.

Appendix

Annex 1. Decomposition of the controlled direct effect of sex on colorectal cancer incidence, effects analysis using log-binomial regressions



Model	Beta	IC 95% Low	IC 95% High
M1	**0.43**	**0.29**	**0.58**
M2	**0.42**	**0.27**	**0.58**
M2a	0.44	0.29	0.59
M2b	0.43	0.28	0.58
M2c	0.42	0.28	0.57
M2d	0.45	0.30	0.59
M2e	0.44	0.30	0.59
M2f	0.44	0.29	0.58
M3	**0.33**	**0.17**	**0.50**
M3a	0.42	0.27	0.57
M3b	0.42	0.26	0.57
M3c	0.40	0.25	0.55
M3d	0.42	0.27	0.58
M3e	0.43	0.28	0.58
M3f	0.38	0.23	0.54
M3g	0.37	0.22	0.53
M3h	0.42	0.27	0.57
M4	**0.30**	**0.13**	**0.46**
M4a	0.33	0.17	0.50
M4b	0.29	0.13	0.46
M4c	0.33	0.17	0.49
M4d	0.33	0.17	0.50

Model 1 (M1): Total Effect of Sex, Overall Effect of Sex at Birth on CRC Incidence adjusting only for competitive exposures (parents' Occupational Classification, parents' ethno-racial background and family history of colorectal cancer) and age at inclusion.

Model 2 (M2): CDE on CRC Incidence adjusting on M1 and block 1; social mediator factors (Partnership status, number of children of the participant, Occupational Classification of individuals, level of education, monthly net household income, French Social Deprivation Index).*

M2a: CDE on CRC Incidence adjusting on M1 and partnership status only.*

M2b: CDE on CRC Incidence adjusting on M1 and number of children of the participant only.*

M2c: CDE on CRC Incidence adjusting on M1 and Occupational Classification of individuals only.*

M2d: CDE on CRC Incidence adjusting on M1 and level of education only.*

M2e: CDE on CRC Incidence adjusting on M1 and monthly net household income only.*

M2f: CDE on CRC Incidence adjusting on M1 and French Social Deprivation Index only.*

Model 3 (M3): CDE on CRC Incidence adjusting on M2 and block 2; behavior mediator factors (balanced diet, consumption of meat, cold cuts, vegetables, fruits, alcohol consumption, smoking status, physical activity).*

M3a: CDE on CRC Incidence adjusting on M2 and balanced diet only.*

M3b: CDE on CRC Incidence adjusting on M2 and consumption of meat only.*

M3c: CDE on CRC Incidence adjusting on M2 and cold cuts only.*

M3d: CDE on CRC Incidence adjusting on M2 and vegetables only.*

M3e: CDE on CRC Incidence adjusting on M2 and fruits only.*

M3f: CDE on CRC Incidence adjusting on M2 and alcohol consumption only.*

M3g: CDE on CRC Incidence adjusting on M2 and smoking status only.*

M3h: CDE on CRC Incidence adjusting on M2 and physical activity only.*

Model 4 (M4): CDE on CRC Incidence adjusting on M3 and block 3; medical and anthropometric mediator factors (personal history of cancer other than CRC, Body Mass Index, type II diabetes and cardiovascular diseases).*

M4a: CDE on CRC Incidence adjusting on M3 and personal history of cancer other than CRC only.*

M4b: CDE on CRC Incidence adjusting on M3 and Body Mass Index only.*

M4c: CDE on CRC Incidence adjusting on M3 and type II diabetes only.*

M4d: CDE on CRC Incidence adjusting on M3 and cardiovascular diseases only.*

**CDE = Controlled Direct Effect of Sex at Birth.*

Annex 2. Effect analyses of model 4, complete model, accounting for interactions between mediators, using logistic regression and comparison of AIC and BIC for model 4 without interactions and model 4 with interactions

Incidence of CRC	Model 4 with interactions		
	β*	[95% IC]	
Women	_	_	_
Men	0.30	[0.13;	0.46]

Model 4	N	AIC	BIC
No interactions	204 172	9256.298	9726.727
Interactions	204 172	9364.275	10990.32

*β = log-odds.

Model 4: Controlled Direct Effect of Sex at Birth on CRC Incidence Adjusting for All Identified Mediating Factors, Early Life Environment, and Age at Inclusion.

LEGEND:

**: interaction CVD: cardiovascular diseases OC: Occupational Classification of individuals.*

For social and behavioral mediator factors.

- diploma*meat/diploma*cold cuts/diploma*alcohol/diploma*tobacco/diploma*physical activity/income*vegetables/income*fruits/OC*alcohol/OC*tobacco

For social and medical mediator factors.

- income*BMI/OC*BMI/income*diabetes

For behavioral and medical mediator factors.

- Diet*BMI/diet*diabetes/alcohol*BMI/alcohol*diabetes/alcohol*personal medical history/physical activity*diabetes/smoking status*diabetes/smoking status*personal medical history

For medical and social mediator factors.

- CVD*income/CVD*socio-professional category/CVD*diploma

For medical and behavioral mediator factors.

- CVD*alcohol/CVD*smoking status/CVD*meat/CVD*cold cuts/CVD*physical activity

For medical mediator factors.

- CVD*diabetes/CVD*BMI

Annex 3. Effects analyses with non-imputed data, on complete cases N = 90 279

Incidence of colorectal cancer		Model 1			Model 2			Model 3			Model 4		
Sex	Women	Ref.	[95 %	CI]	Ref.	[95 %	CI]	Ref.	[95 %	CI]	Ref.	[95 %	CI]
OR	Men	1.30	[1.00;	1.69]	1.31	[1.00;	1.72]	1.22	[0.91;	1.62]	1.14	[0.85;	1.53]
Beta	Men	0.26	[0.00;	0.52]	0.27	[0.04;	0.54]	0.20	[-0.09;	0.48]	0.13	[-0.16;	0.43]

OR:odds ratio of logistic regression.
Beta: coefficient of logistic regression.

Annex 4. Comparison of characteristics between complete cases and a random subsample of the imputed dataset

Variables		Completed cases N = 90 279	Random subsample of database with imputation N = 90 279	P-value Chi-square test
Cases CRC	Yes	230 (0.3 %)	325 (0.4 %)	<0.001
	No	90 049 (100 %)	89 954 (100 %)	
Sex	Men	43 406 (48 %)	41 857 (46 %)	<0.001
	Women	46 873 (52 %)	48 422 (54 %)	
Age at inclusion	<50 years old	56 110 (62 %)	50 499 (56 %)	<0.001
	50–60 years old	17 728 (20 %)	19 246 (21 %)	
	60–75 years old	16 441 (18 %)	20 534 (23 %)	
Partnership status	Single	26 125 (29 %)	25 012 (28 %)	<0.001
	Married or civil partnership	54 077 (60 %)	53 814 (60 %)	
	Separated, divorced, or widowed	10 077 (11 %)	11 453 (13 %)	
Number of child	No children	34 354 (38 %)	34 866 (39 %)	<0.001
	1 child	13 362 (15 %)	13 011 (14 %)	
	2 children	28 129 (31 %)	27 220 (30 %)	
	3 children or more	14 434 (16 %)	15 182 (17 %)	
Fdep	Q1: Very low	18 487 (20 %)	18 107 (20 %)	0.028
	Q2: Low	18 222 (20 %)	17 983 (20 %)	
	Q3: Average	18 083 (20 %)	18 181 (20 %)	
	Q4: High	17 888 (20 %)	18 000 (20 %)	
	Q5: Very high	17 599 (19 %)	18 008 (20 %)	
Occupational Classification (OC)	Disadvantaged OC	32 545 (36 %)	38 263 (42 %)	<0.001
	Advantaged OC	57 734 (64 %)	52 016 (58 %)	
Net monthly household income	Less than 1500€	7,810 (8.7 %)	10 823 (12 %)	<0.001
	From 1500€ to 2100€	9,381 (10 %)	10 868 (12 %)	
	From 2100€ to 2800€	13 195 (15 %)	14 378 (16 %)	
	From 2800€ to 4200€	30 042 (33 %)	28 442 (32 %)	
	4200€ or more	29 851 (33 %)	25 768 (29 %)	
Level of education	Primary degree	4,702 (5.2 %)	8,052 (8.9 %)	<0.001
	Technical degree	11 443 (13 %)	14 497 (16 %)	
	Secondary degree	13 640 (15 %)	14 881 (16 %)	
	University degree: 2 or 3 years	25 684 (28 %)	23 444 (26 %)	
	University degree: master's degree or more	34 810 (39 %)	29 405 (33 %)	
Balanced diet	Yes	75 610 (84 %)	74 220 (82 %)	<0.001
	No	14 669 (16 %)	16 059 (18 %)	
Consumption of meat	Once a week or less	33 004 (37 %)	33 411 (37 %)	0.12
	2 to 3 times a week	34 966 (39 %)	34 807 (39 %)	
	4 times a week or more than once a day	22 309 (25 %)	22 061 (24 %)	
Vegetables	Once a week or less	13 325 (15 %)	13 527 (15 %)	<0.001
	2 to 3 times a week	48 887 (54 %)	48 056 (53 %)	
	4 times a week or more than once a day	28 067 (31 %)	28 696 (32 %)	
Fruits	Once a week or less	17 233 (19 %)	17 376 (19 %)	0.031
	2 to 3 times a week	18 305 (20 %)	17 858 (20 %)	
	4 times a week or more than once a day	54 741 (61 %)	55 045 (61 %)	
Cold cuts	Once a week or less	63 639 (70 %)	64 625 (72 %)	<0.001
	2 to 3 times a week	20 796 (23 %)	19 582 (22 %)	
	4 times a week or more than once a day	5,844 (6.5 %)	6,072 (6.7 %)	
Physical activity	Absent to low	23 584 (26 %)	24 647 (27 %)	<0.001
	Moderate	19 888 (22 %)	19 208 (21 %)	
	High to intense	46 807 (52 %)	46 424 (51 %)	
Alcohol consumption	No consumption	13 723 (15 %)	15 088 (17 %)	<0.001
	Moderate cosumption	67 561 (75 %)	65 858 (73 %)	
	Non-recommended consumption	8,995 (10.0 %)	9,333 (10 %)	
Smoking status	No smoker	42 498 (47 %)	43 229 (48 %)	0.003
	Smoker	16 783 (19 %)	16 562 (18 %)	
	Ex-smoker	30 998 (34 %)	30 488 (34 %)	
Type II diabetes	Yes	1,846 (2.0 %)	2,406 (2.7 %)	<0.001
	No	88 433 (98 %)	87 873 (97,3 %)	
Personal history of cancer other than CRC	Yes	3,758 (4 %)	4,347 (5 %)	<0.001
	No	86 521 (96 %)	85 932 (95 %)	
BMI	Underweight and normal weight	53 588 (59 %)	51 391 (57 %)	<0.001
	Overweight to obesity	36 691 (41 %)	38 888 (43 %)	
Cardiovascular diseases	Yes	12 560 (14 %)	14 609 (16 %)	<0.001
	No	77 719 (86 %)	75 670 (84 %)	
Ethno-racial origin	Majority population	80 572 (89 %)	79 676 (88 %)	<0.001
	Other groups	9,707 (11 %)	10 603 (12 %)	
Parents' Occupation Classification (POC)	Disadvantaged OC	47 341 (52 %)	52 550 (58 %)	<0.001
	Advantaged OC	42 938 (48 %)	37 729 (42 %)	
Family history	CRC	3,652 (4.0 %)	3,756 (4.2 %)	0.002
	Cancer other than CRC	27 547 (31 %)	26 865 (30 %)	
	Absence of information	59 080 (65 %)	59 658 (66 %)	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2025.118058.

Data availability

Data will be made available on request.

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