# Prolonged use of nomegestrol acetate and risk of intracranial meningioma: a population-based cohort study

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## Summary

**Background** Nomegestrol acetate (NOMAC) is a synthetic potent progestogen. This study aimed to assess the risk of intracranial meningioma associated with the prolonged use of NOMAC.

**Methods** Observational cohort study using SNDS data (France). Women included had ≥ one dispensing of NOMAC between 2007 and 2017 (no dispensing in 2006). Exposure was defined as a cumulative dose >150 mg NOMAC within six months after first dispensing. A control group of women (cumulative dose ≤150 mg) was assembled. The outcome was surgery (resection or decompression) or radiotherapy for one or more intracranial meningioma(s). Poisson models assessed the relative risk (RR) of meningioma.

**Findings** In total, 1,060,779 women were included in the cohort (535,115 in the exposed group and 525,664 in the control group). The incidence of meningioma in the two groups was 19.3 and 7.0 per 100,000 person-years, respectively (age-adjusted RRa = 2.9 [2.4–3.7]). The RRa for a cumulative dose of more than 6 g NOMAC was 12.0 [9.9–16.0]. In the event of treatment discontinuation for at least one year, the risk of meningioma was identical to that in the control group (RRa = 1.0 [0.8–1.3]). The location of meningiomas in the anterior and middle part of the skull base was more frequent with exposure to NOMAC.

**Interpretation** We observed a strong dose-dependent association between prolonged use of NOMAC and the risk of intracranial meningiomas. These results are comparable to those obtained for cyproterone acetate, although the magnitude of the risk is lower. It is now recommended to stop using NOMAC if a meningioma is diagnosed.

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**Keywords:** Meningioma; Progestin; Nomegestrol acetate; Pharmacoepidemiology

## Introduction

Nomegestrol acetate (NOMAC) is a synthetic progestin that has been marketed in many European countries since 1985.[1] It is prescribed alone or in combination with an oestrogen at various doses (2.5, 3.75, or 5 mg) as a hormone replacement therapy (HRT) for menopause, treatment of gynaecological menstrual disorders, and treatment of endometriosis (off-label indication)[1] and has been prescribed as an oral contraceptive since 2011 at the 2.5 mg dose (indications detailed in Supplement 1). NOMAC is widely available in Europe (list of countries in Supplement 2), but has never been authorized either in the United States or Canada.

In the general population, meningiomas account for 39.7% of central nervous system tumours and are the most common type of benign intracranial tumour.[2] The

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## Research in context

### Evidence before this study

We searched PubMed from Jan 1, 1996, to July 1, 2023, with the terms {"nomegestrol" or "progestogen"} and"meningioma". We restricted the search to reviews and studies published in English or French. Meningiomas are the most common of intracranial tumours. They are generally histologically benign but may, nevertheless, be symptomatic or growing and require surgical removal or radiotherapy. The identified risk factors of meningioma are age, female gender, neurofibromatosis type 2, and exposure to previous cerebral radiation therapy.

Numerous studies support a biologically plausible association between progesterone and intracranial meningioma. Some, but not all, reported an increase in the risk of developing meningioma with hormonal therapy for menopause, including progestogens. More recently, the risk of meningioma and the use of cyproterone acetate, a potent progestogen, at high doses was established.

Nomegestrol acetate (NOMAC) is a synthetic progestogen with powerful progestative activity at doses of 3.75 and 5 mg and is marketed in Europe (France, Italy, Portugal, Belgium, Luxembourg, and Poland). In France, several case-reports of intracranial meningiomas following prolonged exposure to NOMAC have been published, but no epidemiological study has yet assessed the dose–response relationship between the use of NOMAC and meningioma development.

### Added value of this study

This study shows a strong, dose-dependent association between the use of NOMAC (3.75 or 5 mg) and meningioma treated by surgery or radiotherapy.

For the largest class of cumulative doses of NOMAC considered (6 g and above), the risk of meningioma was multiplied by 12. For the cumulative dose 1.2 g–3.6 g, the risk was more than doubled.

The risk of meningioma among women who discontinued NOMAC for at least one year, without restarting use, was not significantly different from that of the control group, provided that the cumulative dose before cessation was less than 1.2 g.

As with cyproterone acetate, meningiomas located in the anterior and middle part of the skull base were particularly associated with prolonged exposure to NOMAC.

### Implications of all the available evidence

Women using NOMAC (5 or 3.75 mg) for several years should be informed of the increased risk of developing intracranial meningiomas. The indication for NOMAC should be well-defined and justified, using the lowest possible dose and the shortest possible duration of use.

In the case of prolonged use of NOMAC, regular screening for meningiomas by magnetic resonance imaging should be recommended.

If a meningioma is diagnosed in a patient currently under NOMAC treatment, it should be permanently discontinued and the patient should undergo a neurosurgical follow-up. Indeed, the meningioma may regress in response to treatment discontinuation and invasive surgical treatment avoided. Prescribers must also be vigilant about switching to other progestogens, which could also carry an increased risk of developing meningioma.

main identified risk factors for meningioma are female gender, age, exposure to ionizing intracranial radiation, and neurofibromatosis type 2.[3] In addition to these factors, there is a long history of studies focusing on the association between these tumours and female sex hormones. Several relevant studies have shown a higher frequency of meningiomas among women (sex-ratio of up to 3.5:1 at approximately 40 years of age[3]), faster growth of these tumours during pregnancy and the tendency to shrink after delivery,[4] and the presence of progesterone receptors in meningiomas.[5] Concerning exogenous hormones, numerous epidemiological studies have been carried out, showing a strong dose-dependent association between the occurrence of meningioma and the use of cyproterone acetate (CPA), a potent progestogen,[6] with frequent regression of tumour volume after treatment discontinuation.[7,8] Several studies found association between the occurrence of meningiomas and hormone replacement therapy[9,10] but no association with oral contraception.[11–13]

In 2018 and 2019, Froelich et al. from Lariboisière AP-HP Paris Hospital described for the first time a possible relationship between the risk of developing meningioma in women and the prolonged exposure of NOMAC.[14,15] In 2018, Champagne et al. first described changes in meningioma volume for a 46-year-old woman that correlated with her use of NOMAC and CPA.[14] Then, in 2019, four cases of intracranial meningioma associated with exposure to NOMAC were reported with partial regression of the meningiomas after discontinuation, which is suggestive of the role of this drug in the development of these brain tumours.[15] In terms of their location, the meningiomas were situated in the middle of the skull base, the clivus, and the frontal convexity.[15]

A French Scientific Committee on meningioma and progestogen under the responsibility of the French medicine agency (ANSM) requested this present study from EPI-PHARE.

Our main objective was to assess the impact of prolonged use of NOMAC (3.75, 5 mg) on the risk of meningioma among women in the French population. Our secondary objectives were to assess the dose-effect relationship, define the evolution of meningioma risk

after NOMAC discontinuation, and identify the specific characteristics of meningiomas associated with NOMAC use. The results of this study were forwarded to the European Medicines agency (EMA) in accordance with the usual procedure.

## Methods

### Study design and data source
This observational population-based study followed a cohort design and was based on data derived from the French national health data system (*Système National des Données de Santé*, SNDS). The SNDS database contains information on all health reimbursements for over 99.5% of the population residing in France and is linked to the French hospital discharge database that provides data on all hospital admissions and diagnoses (according to the International Statistical Classification of Diseases and Related Health Problems, ICD-10). Drugs are coded with a bar code entry (CIP) and recoded automatically according to the Anatomical, Therapeutic and Chemical Code (ATC).

The SNDS is currently one of the largest healthcare databases in the world and is used frequently in pharmacoepidemiological studies in women health.[6,16–18]

### Study population
The study focused on a cohort of women who initiated NOMAC between 2007 and 2017 affiliated with the general national health insurance scheme (covering 87% of the French population) and aged between 10 and 70 years at the time of NOMAC initiation, to include all women for whom this treatment is indicated (ATC G03DB04, G03FB12; Supplement 3).

Women with neurofibromatosis type 2 (ICD-10 codes Q85.0), a history of benign brain tumour (ICD-10 codes C70, D32, D33, D42), a NOMAC dispensing in 2006, a lack of data in the year before the first NOMAC dispensing, or who had received progestogens known to increase the risk of meningioma (CPA (ATC G03HA01) and CMA (chlormadinone acetate, ATC G03DB06), codes in Supplements 4 & 5) were excluded from the study.

Women are identified by their personal smart card, with daily teletransmission of healthcare acts performed by health professionals to the French national health insurance organization. We focused on cis-gender women, as NOMAC is not indicated for men and not used or recommended for transgender women.

### Definition of exposure
Women were considered to be "exposed" if they had had a first dispensation of NOMAC (3.75 or 5 mg, ATC G03DB04, G03FB12, codes in Supplement 3) between 1 January 2007 and 31 December 2017, without any dispensing in 2006, and had received a cumulative dose of more than 150 mg within the six months following the first dispensation.

The remaining women were considered to be "slightly exposed" to NOMAC (cumulative dose ≤150 mg within the first six months) and they constituted the control group. A cumulative dose of 150 mg corresponds to a maximum of three months' treatment (three boxes or less). Thus the control group included women who stopped treatment prematurely (dosage threshold already used in previous work[6]; indications and dosage schedules are detailed in Supplement 1). Women of the exposure group were considered to have discontinued NOMAC treatment after one year without NOMAC dispensing. We also assembled a "discontinued group", among women in the exposed group.

### Definition of the outcome
The outcome was hospitalization for one or more intracranial meningiomas with aggressive treatment (surgery or radiotherapy). The outcome was identified as a first hospitalization with a diagnosis of meningioma (ICD-10: D32, coded as main or related diagnosis) combined with at least one procedure for tumour removal or other related surgeries, stereotactic radiosurgery, or fractionated radiation therapy during the same hospital stay (detailed codes in Supplements 6 & 7). For clarity, we will refer to the outcome as "meningioma(s)" rather than "hospital treatment for meningioma".

To assess neurosurgical reoperations in the first or second year after the initial surgery, we eliminated meningiomas occurring in 2017 and 2018 (to have a sufficient look-back period). We thus calculated the number of new occurrences of meningioma (other location) or recurrences of meningioma (same location as the first surgery) in the same subject among meningiomas occurring before 2017.

### Study period
The index date corresponded to the date of first dispensation of NOMAC. We also defined a period of follow-up beginning six months after the index date.

All participants were followed until 31 December 2018 at the latest. The follow-up ended at the earliest occurrence of the following events: occurrence of meningioma, "loss to follow-up" (defined by a period of more than 24 months without any healthcare reimbursement), dispensation of CPA (50 or 100 mg) and/or CMA (2, 5, or 10 mg), pregnancy, restarting NOMAC for the control group, discontinuation of NOMAC for one year for the exposed group, or death.

### Covariates
The following characteristics of the women were considered: sociodemographic characteristics (age in five classes (10–24, 25–34, 35–44, 45–54, 55+ years of age), affiliation with the C2S/CMUc (a complementary universal health insurance plan that provides free access to healthcare if the annual income is less than €9,719 for a single person), specialty of the initial prescriber

(gynaecologist, general practitioner, others), and co-prescription of oestrogens (Supplement 8).

The anatomical location of the meningiomas was determined based on the CCAM code (*Classification Commune des Actes Médicaux*/classification for medical procedures). The meningiomas were divided among five locations (anterior skull base, middle skull base, posterior skull base, convexity, falx cerebri and tentorium) (Supplement 6).

## Statistical analyses

Data were analysed using SAS software version 9.4 (SAS Institute Inc.).

For the primary analysis, Poisson regression were used to compare the outcome rates between the exposed and control groups. Two categories of exposure were analysed: a fixed binary classification (either "exposed" or "control") and the cumulative dose of NOMAC as a time-varying factor within the exposed group. A p value < 0.05 was considered statistically significant (two-tailed tests).

Similarly, we also compared the exposed, control, and discontinued groups in a three-group analysis and assessed the effects based on cumulative doses. Group assignment was time varying. Indeed, for this analysis, in the control group, receiving a new NOMAC prescription led to reclassification into the "exposed" group. Conversely, in the "exposed" group, discontinuing treatment for a year moved patients into the "discontinued" group.

Adjustments were made for age, expressed as a time-dependent variable, and baseline characteristics (C2S/CMUc, medical specialty of the initial prescriber, co-prescription of oestrogens), retaining only variables statistically significantly associated with the meningioma outcome. The cumulative dose and age were treated as time-dependent variables in the analysis.

Four sensitivity analyses were performed. The first consisted of a Cox model to assess the hazard ratio adjusted for age as a time-dependent variable to help readers visualize the risk gap between exposed and controls groups. The second consisted of a nested case–control design and was conducted to assess sensitivity with respect to the differences in the end-of-follow-up criteria between the exposed and control groups. Each case was matched with 30 controls for age (±1 year) and duration of follow-up using the risk set sampling method (each control retained on a given index date was alive on that date and was not a case in the past, but could become a case in the future).[17] Thus, the duration of follow-up of the controls was equal to that of their corresponding case. This approach estimated the odds ratio for exposure and meningioma occurrence via conditional logistic regression. The third sensitivity analysis estimated the risk of meningioma within a subgroup of women without a co-prescription of oestrogen, and the fourth sensitivity analysis estimated the risk excluding women with a history of malignant brain tumour.

Finally, as a complementary analysis, we performed a comparison with an age-matched (subjects matched for year of birth) control group of patients who did not receive NOMAC (hereafter referred to as "non-exposed"). Each matched subject pair was censored by the pair's minimum end-of-follow-up value.

## Ethics

This present study complies with the STROBE statement and was authorized by decree 2016–1871 on December 26, 2016.[19] As an authorized permanent user of the SNDS, the author's team was exempt from approval from the institutional review board.

The study was declared before implementation in the register of studies of the EPI-PHARE Scientific Interest Group with register reference T-2019-07-165.

## Role of the funding source

## Results

### Description of the study population

In total, 1,648,035 women living in France (Western Europe) initiated NOMAC between 1 January 2007 and 31 December 2017. After application of the exclusion criteria, 1,060,779 women were included in the cohort: 535,115/1,060,779 (50.4%) in the exposed group and 525,664/1,060,779 (49.6%) in the control group (Fig. 1).

The average age of the women was 39.6 years [Standard Deviation: 10.3] (Table 1). The initial prescriber of NOMAC was generally a gynaecologist (569,690/1,060,779, 52.7%) or general practitioner (461,490/1,060,779, 43.5%).

The exposed population and control group showed differences at inclusion. Women in the exposed group were slightly older (average age: 40.9 years [SD: 9.7] vs 38.2 [10.7]), socially less disadvantaged (affiliation to CMUc: 11.2% (60,116/535,115) vs 18.0% (94,428/525,664)), and more often started treatment with a gynaecologist (57.5% (307,433/535,115) vs 48.2% (253,257/525,664)). A co-prescription of oestrogen was found for 53,393/1,060,779 individuals (5.0%) (24,836/535,115 in the exposed group [4.6%] and 28,557/525,664 in the control group [5.4%]). On average, women had taken a cumulative dose of NOMAC of 283 mg [SD: 256]
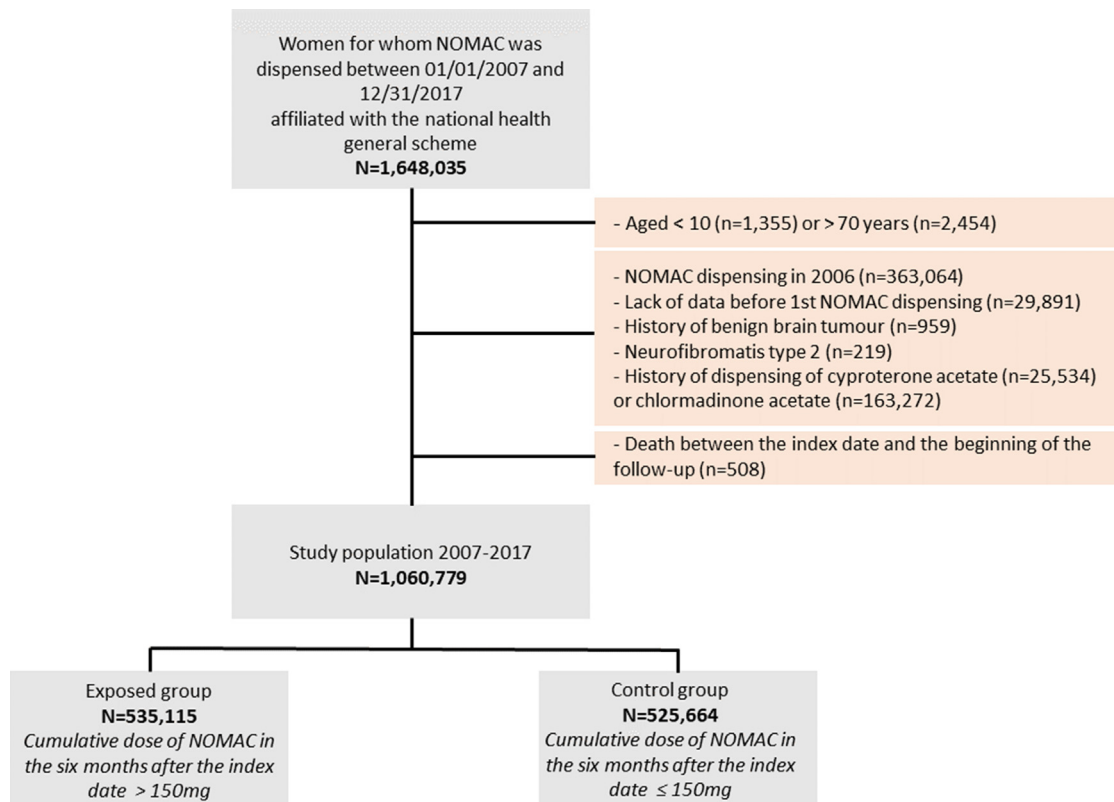
**Fig. 1:** Flowchart of the study population. Abbreviations: mg, milligrams; NOMAC, nomegestrol acetate. The index date is the date of the first nomegestrol acetate dispensing.

at the start of follow-up (467 mg [246] for the exposed women and 96 mg [37] for the controls, respectively).

The average follow-up was 1.7 years [SD 1.6] for women in the exposed group and 4.6 years [3.5] for women in the control group. In total, the person-years of follow-up reached 3,303,332, with 884,716 for the exposed group and 2,418,616 for the control group.

Most women (430,699/535,115, 80.5%) in the exposed group left the cohort before 12/31/2018 due to treatment discontinuation of more than one year, whereas less than a sixth (85,610/525,664, 16.3%) of the control group left the cohort for the treatment resumption. Finally, 28,339/535,115 women were exposed to NOMAC for more than five years.

### Risk of meningioma(s)

Age was strongly associated with the risk of meningioma. Relative to the 25–34 year age group, the RR was significantly higher for those aged 35–44 (RR = 3.2 [1.7–6.0]), 45–54 (RR = 4.7 [2.5–8.6]), and 55 and older (RR = 5.8 [3.0–10.8]) (Supplement 9). None of the variables tested after age adjustment, including affiliation to the CMUc, prescriber specialty, or simultaneous oestrogen prescription, were significantly associated with

the risk of meningioma. In this context, the only adjustment we made was for age (considered as a time-dependant variable) as an effect modifier.

There were 171 women with meningiomas for 884,716 person-years in the exposed group and 169 for 2,418,616 person-years in the control group. The crude incidence rates for the two groups were 19.3 and 7.0 per 100,000 person-years, respectively, resulting in a crude RR of 2.8 [2.2–3.4] and an age-adjusted RR of 2.9 [2.4–3.7] (Fig. 2). The results showed a positive multiplicative interaction between NOMAC exposure and age: as age increases, so does the effect of NOMAC exposure (Supplements 10 and 11).

Analysis by cumulative dose of NOMAC showed a strong dose-effect relationship; the higher the cumulative dose, the higher the risk of meningioma (Fig. 2). The incidence reached approximately 91.5 cases per 100,000 person-years in the group with a cumulative exposure of >6 g NOMAC. Beyond cumulative exposure to 1.2 g NOMAC, the risk increased significantly with the cumulative dose, reaching an age-adjusted RR of 12.0 [9.9–16.0] for >6 g NOMAC. We also observed that the incidence and relative risk of meningioma depended on the duration of NOMAC exposure (Supplement 12).

| | Exposed N = 535,115 | Controls N = 525,664 |
|---|---|---|
| | N (%) | N (%) |
| **Age (years) at initiation** | | |
| Mean age (SD) | 40.9 (9.7) | 38.2 (10.7) |
| Median age [IQR] | 43 [36–48] | 40 [30–47] |
| 10–24 | 43,202 (8.1) | 69,723 (13.3) |
| 25–34 | 77,813 (14.5) | 111,489 (21.2) |
| 35–44 | 184,862 (34.5) | 168,333 (32.0) |
| 45–54 | 214,534 (40.1) | 162,539 (30.9) |
| ≥55 | 14,704 (2.7) | 13,580 (2.6) |
| **Year of initiation of NOMAC** | | |
| 2007–2010 | 252,783 (47.3) | 250,481 (47.6) |
| 2011–2014 | 179,759 (33.6) | 178,094 (33.9) |
| 2015–2017 | 102,573 (19.2) | 97,089 (18.5) |
| **C2S/CMUc beneficiary[a]** | | |
| Yes | 60,116 (11.2) | 94,428 (18.0) |
| **Initial prescriber's specialty** | | |
| Gynaecologist | 307,433 (57.5) | 253,257 (48.2) |
| General practitioner | 207,099 (38.7) | 254,391 (48.4) |
| Others | 14,898 (2.8) | 13,353 (2.5) |
| Missing data | 5685 (1.1) | 4663 (0.9) |
| **Oestrogen co-prescription** | | |
| Yes | 24,836 (4.6) | 28,557 (5.4) |
| **Cumulative NOMAC dose at start of follow-up (mg)[b]** | | |
| Mean (SD) | 467 (246) | 96 (37) |
| Median [IQR] | 400 [300–630] | 100 [50–105] |
| **Duration of follow-up (years)** | | |
| Mean duration (SD) | 1.7 (1.6) | 4.6 (3.5) |
| Median duration [IQR] | 1.0 [1.0–1.6] | 3.9 [1.4–7.6] |
| <2 years | 432,419 (82.1) | 169,647 (32.8) |
| [2 years; 5 years] | 74,357 (14.1) | 137,051 (26.5) |
| [5 years; 8 years] | 20,396 (3.9) | 101,042 (19.6) |
| ≥8 years | 7943 (1.5) | 117,924 (22.8) |
| Person-years (PY) | 884,716 | 2,418,616 |
| **Event/reason for censoring** | | |
| At 31/12/2018 | 48,446 (9.1) | 307,925 (58.6) |
| Death | 1164 (0.2) | 3571 (0.7) |
| Outcome (meningioma) | 171 (0.0) | 169 (0.0) |
| Pregnancy | 22, 592 (4.2) | 85, 718 (16.3) |
| Cyproterone acetate[c] | 2338 (0.4) | 3167 (0.6) |
| Chlormadinone acetate[c] | 29,705 (5.6) | 28,660 (5.5) |
| Discontinuation of exposure | 430,699 (80.5) | – |
| Lost to follow-up[d] | – | 10,844 (2.1) |
| New dispensing (control group) | – | 85,610 (16.3) |

[a]C2S/CMUc: complementary universal health insurance plan that provides free access to healthcare if the annual income is less than €9,719 for a single person. [b]In the six months after the index date. [c]End of follow-up at first dispensation of cyproterone or chlormadinone acetate. [d]Women were considered "lost to follow-up" when no health reimbursements were recorded in two years. In the exposed group, a NOMAC discontinuation >1 year was classified as "discontinuation of exposure" (i.e., before the period of two years corresponding to "lost to follow-up").

*Table 1:* **Characteristics of exposed and control groups in the study period 2007–2017 (N = 1,060,779).**

The sensitivity analysis using a Cox model (Fig. 3 and Supplement 13), a nested case–control design within the cohort (Supplement 14) provided very similar estimates. The amplitude of the risk of meningioma was not modified by excluding women with a co-prescription of oestrogen at the index date (Supplement 15) and by excluding women with history of malignant cerebral tumours (n = 344 women, Supplement 16).

Finally, we have matched 535,115 exposed women with 535,115 non-exposed women (never been exposed to NOMAC) for year of birth. The mean duration of follow-up was 1.6 years [SD: 1.5] (836,804 person-years in each group). The crude incidence rates were 19.2 and 8.2 per 100,000 person-years for exposed and not-exposed group, respectively. We obtained similar results than the main analysis using an age-matched cohort of women who have never been exposed to NOMAC with an age-adjusted RR of 2.3 [1.7–3.0] (Supplement 17).

### Effect of treatment discontinuation
Overall, the risk of meningioma after one year of discontinuing NOMAC was not significantly higher than that in the control group (RRa 1.0 [0.8–1.3]). However, the risk was 1.5 times [1.1–2.2] higher when the cumulative dose of NOMAC before discontinuation reached 1.2 g or more (Fig. 2).

Of note, the higher number of cases observed in the exposed group based on the 3-group sensitivity analysis (210 cases) than that in the exposed group based on the 2-group main analysis (171 cases) was due to the management of exposure as a time-dependent variable in the 3-group analysis. Indeed, 39 women initially classified in the main analysis subsequently restarted taking NOMAC and developed a meningioma, resulting in 210 women with meningioma in exposed group instead of 171 in exposed group in the main analysis. The follow-up of these 39 women was censored on resumption of treatment in the main analysis.

### Description of the meningioma characteristics
The clinical characteristics and therapeutic management of meningioma are presented in Table 2. Most of the treatment consisted of resection or decompression surgery, which were performed more frequently for exposed women than women in the control group (161/171, 94.2%, vs 144/169, 85.2%, respectively). The median age at the time of meningioma treatment was two years less for the exposed group (49 [IQR 45–53] vs 51 years [45–55]), contrasting with a higher age at initiation (median 43 years vs 40).

There was a significant difference in the location of the meningioma surgery between the exposed and control groups. Anterior skull base tumours were more frequent in the exposed group than in the control group (47/171, 29.2% vs 25/169, 17.4%), similarly to middle skull base tumours (53/171, 32.9% vs 34/169, 23.6%). Conversely, there was a higher proportion of convexity
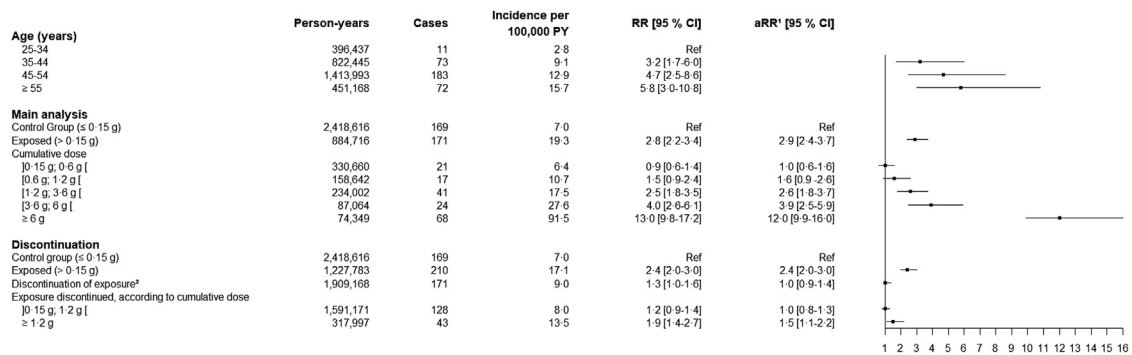
| Age (years) | Person-years | Cases | Incidence per 100,000 PY | RR [95 % CI] | aRR¹ [95 % CI] |
|---|---|---|---|---|---|
| 25-34 | 396,437 | 11 | 2·8 | | |
| 35-44 | 822,445 | 73 | 9·1 | 3·2 [1·7-6·0] | |
| 45-54 | 1,413,993 | 183 | 12·9 | 4·7 [2·5-8·6] | |
| ≥ 55 | 451,168 | 72 | 15·7 | 5·8 [3·0-10·8] | |
| **Main analysis** | | | | | |
| Control Group (≤ 0·15 g) | 2,418,616 | 169 | 7·0 | Ref | Ref |
| Exposed (> 0·15 g) | 884,716 | 171 | 19·3 | 2·8 [2·2-3·4] | 2·9 [2·4-3·7] |
| Cumulative dose | | | | | |
| ]0·15 g; 0·6 g [ | 330,660 | 21 | 6·4 | 0·9 [0·6-1·4] | 1·0 [0·6-1·6] |
| [0·6 g; 1·2 g [ | 158,642 | 17 | 10·7 | 1·5 [0·9-2·4] | 1·6 [0·9 -2·6] |
| [1·2 g; 3·6 g [ | 234,002 | 41 | 17·5 | 2·5 [1·8-3·5] | 2·6 [1·8-3·7] |
| [3·6 g; 6 g [ | 87,064 | 24 | 27·6 | 4·0 [2·6-6·1] | 3·9 [2·5-5·9] |
| ≥ 6 g | 74,349 | 68 | 91·5 | 13·0 [9·8-17·2] | 12·0 [9·9-16·0] |
| **Discontinuation** | | | | | |
| Control group (≤ 0·15 g) | 2,418,616 | 169 | 7·0 | Ref | Ref |
| Exposed (> 0·15 g) | 1,227,783 | 210 | 17·1 | 2·4 [2·0-3·0] | 2·4 [2·0-3·0] |
| Discontinuation of exposure² | 1,909,168 | 171 | 9·0 | 1·3 [1·0-1·6] | 1·0 [0·9-1·4] |
| Exposure discontinued, according to cumulative dose | | | | | |
| ]0·15 g; 1·2 g [ | 1,591,171 | 128 | 8·0 | 1·2 [0·9-1·4] | 1·0 [0·8-1·3] |
| ≥ 1·2 g | 317,997 | 43 | 13·5 | 1·9 [1·4-2·7] | 1·5 [1·1-2·2] |

**Fig. 2: Incidence and relative risk of meningioma according to cumulative exposure to nomegestrol acetate, and discontinuation of exposure**. [1]Adjustment for age; cumulative dose and age considered as time-dependent variable. [2] > One year. Abbreviations: 95% CI, confidence interval; RR, relative risk. The first age category (10–24 years old, 1 outcome, RR = 0.2 [0.0–1.3]) is not represented for the purposes of forest plot width.
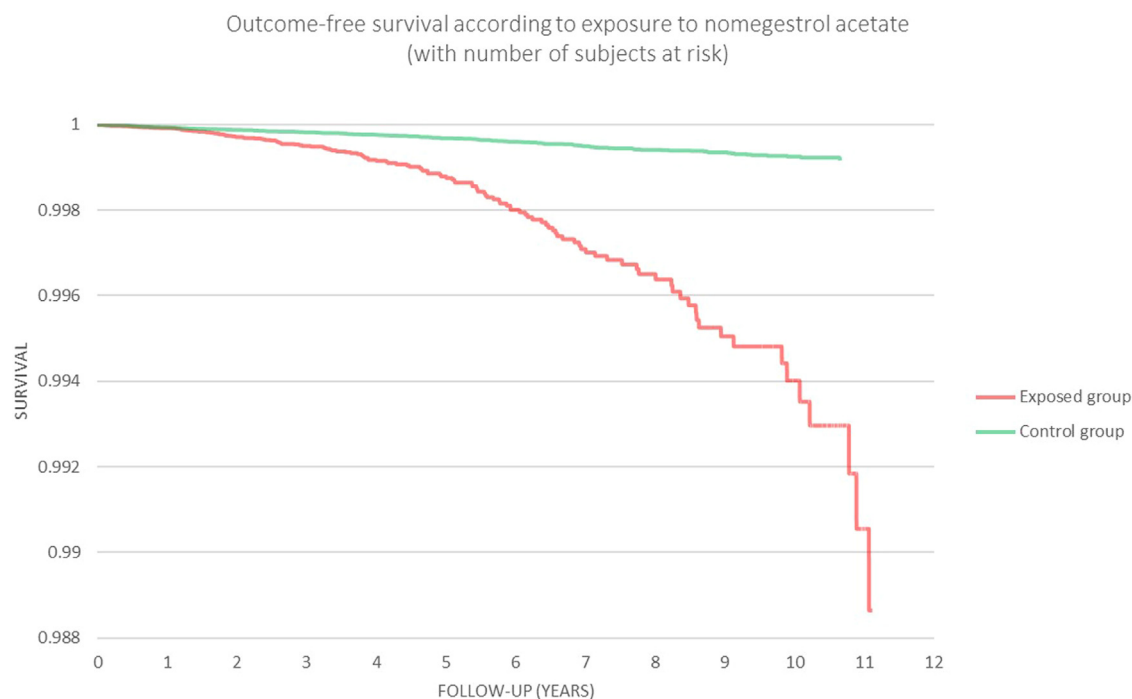


Outcome-free survival according to exposure to nomegestrol acetate (with number of subjects at risk)

| Years | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Numbers at risk** | Exposed | 535,115 | 218,952 | 102,696 | 62,834 | 41,669 | 28,339 | 19,048 | 12,563 | 7,943 | 4,671 | 2,240 | 630 | 0 |
| | Controls | 525,664 | 427,274 | 356,017 | 301,999 | 257,714 | 218,966 | 183,681 | 150,100 | 117,924 | 85,868 | 52,804 | 18,873 | 0 |

**Fig. 3: Kaplan Meier plot on timing of meningioma and censoring for the control group and the exposed group.**

tumours in the control group (48/169, 28.4% vs 35/171, 20.5%).

In total, 264 meningiomas occurred before 2017 (instead of 340 meningiomas for the whole study period): 136 in the exposed group and 128 in the control group. Among the controls, no new occurrence or recurrence of meningioma in the same person was observed. In the exposed group, 6/136 (4.4%) were reoperated on in the first year and 2/136 (1.5%) in the second year after the first surgery.

Lastly, the meningioma group exposed to NOMAC differed from the control group by having significantly

| | All N = 340 | Exposed N = 171 | Controls N = 169 | p-value (Fisher Exact Test) |
|---|---|---|---|---|
| Initial treatment | | | | 0.010 |
| Neurosurgery | 305 (89.7) | 161 (94.2) | 144 (85.2) | |
| Radiotherapy | 35 (10.3) | 10 (5.8) | 25 (14.8) | |
| Age at treatment of meningioma | | | | <0.0001 |
| Mean age (SD) | 49.3 (7.1) | 48.7 (6.0) | 50.0 (7.9) | |
| Median age [IQR] | 51 [45–54] | 49 [45–53] | 51 [45–55] | |
| 10–24 | 1 (0.3) | 0 (0) | 1 (0.6) | |
| 25–34 | 11 (3.2) | 3 (1.8) | 8 (4.7) | |
| 35–44 | 73 (21.5) | 42 (24.6) | 31 (18.3) | |
| 45–54 | 183 (53.8) | 104 (60.8) | 79 (46.7) | |
| 55–64 | 72 (21.2) | 22 (12.9) | 50 (29.6) | |
| 65 and over | 0 (0) | 0 (0) | 0 (0) | |
| Coprescription of oestrogens | | | | 0.36 |
| Yes | 19 (5.6) | 12 (7.0) | 7 (4.1) | |
| Duration of follow-up | | | | 0.23 |
| Less than 2 years | 122 (35.9) | 69 (40.4) | 53 (31.4) | |
| [2–5 years] | 99 (29.1) | 46 (26.9) | 53 (31.4) | |
| 5 years and longer | 119 (35.0) | 56 (32.7) | 63 (37.3) | |
| Cumulative dose | | | | <0.0001 |
| ≤0.15 g | 169 (49.7) | 0 (0) | 169 (100) | |
| ]0.15 g; 0.6 g[ | 21 (6.2) | 21 (12.3) | 0 (0) | |
| [0.6 g; 1.2 g[ | 17 (5.0) | 17 (9.9) | 0 (0) | |
| [1.2 g; 3.6 g[ | 41 (12.1) | 41 (24.0) | 0 (0) | |
| [3.6 g; 6 g[ | 24 (7.1) | 24 (14.0) | 0 (0) | |
| 6 g and higher | 68 (20.0) | 68 (39.8) | 0 (0) | |
| Anatomical site of meningioma | | | | 0.0074 |
| Group 1: Anterior skull base | 72 (23.6) | 47 (29.2) | 25 (17.4) | |
| Group 2: Middle of skull base | 87 (28.5) | 53 (32.9) | 34 (23.6) | |
| Group 3: Posterior skull base | 34 (11.1) | 14 (8.7) | 20 (13.9) | |
| Group 4: Convexity | 83 (24.4) | 35 (20.5) | 48 (28.4) | |
| Group 5: Falx and tentorium | 29 (9.5) | 12 (7.5) | 17 (11.8) | |
| Missing (no surgery) | 35 | 10 | 25 | |
| Length of hospital stay for initial treatment (days) | | | | 0.18 |
| Median duration (IQR) | 7 (6–10) | 7 (6–9) | 7 (6–10) | |
| Less than 7 days | 124 (36.5) | 55 (32.2) | 69 (40.8) | |
| 7–9 days | 130 (38.2) | 75 (43.9) | 55 (32.5) | |
| 10 days and longer | 86 (25.3) | 41 (24.0) | 45 (26.6) | |
| Death | | | | |
| Deaths at 30 days | 2 (0.6) | 1 (0.6) | 1 (0.6) | 1.0 |
| Deaths at 1 year | 3 (0.9) | 2 (1.2) | 1 (0.6) | 1.0 |
| Use of antiepileptic drug treatment[a] | | | | |
| From date of discharge to 1 year | 147/264 (55.7) | 68/136 (50.0) | 79/128 (61.7) | 0.073 |
| 1 year to 2 years after discharge | 82/264 (31.1) | 33/136 (24.3) | 49/128 (38.3) | 0.020 |
| Hospitalisation for seizures[a] | | | | |
| From date of discharge to 1 year | 6/264 (2.3) | 3/136 (2.2) | 3/128 (2.3) | 1.0 |
| 1 year to 2 years after discharge | 1/264 (0.4) | 0 (0) | 1/128 (0.8) | 0.97 |
| Neurosurgical reoperation[a,b] | | | | |
| From date of discharge to 1 year | 6/264 (2.3) | 6/136 (4.4) | 0/128 (0) | 0.035 |
| 1 year to 2 years after discharge | 2/264 (0.8) | 2/136 (1.5) | 0/128 (0) | 0.53 |

Abbreviations: CCAM, Classification Commune des Actes Médicaux (common classification for medical acts); IQR, Interquartile range; SD, standard deviation. [a]Neurosurgical reoperation designates a new occurrence or the recurrence of a meningioma. [b]For neurosurgical revision, only meningiomas occurring in 2007–2016 were considered to have a sufficient look-back period.

*Table 2*: Description of characteristics of the meningiomas.

less use of antiepileptics beyond a year after the procedure (33/171, 24.3% vs 49/169, 38.3%).

## Discussion

This population-based study demonstrates a strong dose-dependent association between prolonged use of the progestogen NOMAC and intracranial meningioma risk.

Above a cumulative dose of 1.2 g of NOMAC, the risk of meningioma doubled, and was multiplied by 12 above a cumulative dose of 6 g (i.e., treatment of approximately five years). Stopping NOMAC treatment for one year resulted in the absence of excess risk of meningioma requiring an aggressive medical procedure. Finally, meningiomas of women exposed to NOMAC were more frequently located in the anterior and middle skull base.

Comparison with our recent study on CPA[6] shows that the real-life risk of meningioma is lower with NOMAC than CPA (absolute risk = 19.3 per 100,000 person-years and RRa = 2.9 [2.4–3.7] for NOMAC vs 23.8 per 100,000 person-years and an adjusted hazard ratio of 6.6 [4.0–11.1] for CPA). However, the age of the individuals taking NOMAC was higher (40 vs 30 years) than those taking CPA, and NOMAC was more commonly used, two reasons for an expected higher risk in real-life conditions. Another progestogen, CMA, has also been found to be associated with meningioma risk in a French case–control study on the same database SNDS (OR = 4.7 [4.5–5.3]), with a slightly lower magnitude of risk than that for NOMAC found in this other study (OR = 6.5 [5.8–7.2]).[20]

The amplitude of risk of developing meningioma observed in this present study for NOMAC is much greater than that shown in previous studies on menopausal HRT. The meta-analysis of Benson et al. showed indeed a significantly increased risk of meningioma with HRT (with a whole range of progestogens other than NOMAC), with a relative risk of 1.35 [1.22–1.49].[9] However other studies have given contradictory results regarding HRT and meningioma risk,[21] and none has shown a risk in relation to progestin-based contraception at the time of our study.[22,23]

A class effect of progestogens is probable and further studies on the risk of meningioma associated with other less potent progestogens are needed.

Our study provides new data concerning the effects of sex hormones on meningioma risk. The risk of meningioma appears to be well borne by the progestogen, independently of the concomitant prescription of oestrogens. The substantial magnitude of risk, potent dose–response relationship, particularity of tumour location, and risk reduction following NOMAC cessation provide evidence of a likely causal relationship.

The presence of progesterone receptors is found in most meningiomas and are believed to play a significant role in tumor growth. Several authors have reported a heterogeneous distribution of progesterone receptors according to the site of the meningioma.[24] Recently, Okano et al.[25] demonstrated that specific oncogenic mutations and characteristics of meningiomas (tumour location, histological findings whose progesterone receptors) were related to the site of origin of the meninges from which meningiomas arise and CPA-related meningiomas often present a higher PR expression than non-CPA-induced meningiomas.[26] Our study identified a predominance of NOMAC-associated meningiomas in this region, in accordance with these findings. Beyond the location and expression of progesterone receptors, other previous monocentric studies have identified common histological patterns for meningiomas exposed to progestogens (predominance of transitional sub-types, a specific mutational landscape with a high rate of PI3K mutation and low rate of NF2 mutation, and low oestrogen receptor expression).[27,28]

Surgical resection of meningioma arising from the skull base is more challenging than those located in the convexity, considering their closed relationship with critical neurovascular structures that may hamper the extent of resection. Our results also indicate a substantial proportion of women who underwent re-operation and used antiepileptic drugs, even long after the initial surgery. Meningiomas at the base of the skull are most often R1-resected (i.e., Resection margin 1: "R1–cancer cells present microscopically at the primary tumour site") due to the difficult surgical conditions. We did not have access to the details of the resections, but as R1-resection is known to be the most important prognostic factor for the recurrence of meningiomas, a higher rate of neurosurgical reoperations among women exposed to NOMAC could be expected relative to the controls.

It is thus crucial to detect NOMAC-exposed meningiomas by cerebral imaging before they become symptomatic to avoid surgery. In the event that a meningioma is discovered, discontinuing NOMAC with a closed follow-up represent the first line of treatment. Certain patterns of NOMAC use seem to differ according to the age of the user and the indication. The potentially lengthy use of progestogens by young women with chronic disorders (such as endometriosis) or off-label indications, results in a significant cumulative dose that must be taken into account. The more occasional use of progestogens in the perimenopause period, but at an age when meningiomas are more common, is also a major issue.

Women using NOMAC for several years should be informed of the increased risk of developing meningiomas. The benefit-risk balance must be clearly established and explained. The indication for NOMAC should be justified, and in the case of prolonged use of NOMAC, regular screening for meningiomas by imaging should be recommended. Finally, switching to other treatments should also be considered.

This population-based study provides new information on the dose-effect relationship between the use of NOMAC and intracranial meningioma. To avoid

misclassification bias and ensure high outcome specificity, we chose to use a combination of hospital diagnoses associated with interventional neurosurgery or radiotherapy of meningioma. Over 90% of meningiomas requiring hospital treatment involved surgery, validating the diagnoses based on histological tests and thus eliminating the inclusion of other brain tumours. This methodology sidesteps the pitfalls of relying on varying spontaneous reports by healthcare professionals. This cohort was also assembled from a wide population, in which exposure to NOMAC was measured prospectively over the study period, excluding recall bias. The inclusion of new users under real-life conditions allowed us to estimate both the absolute and relative risk. This type of data is necessary to objectively inform patients and help them and healthcare professionals decide on the actions to take. The analyses took into account the differences in the duration of follow-up between groups and were adjusted for age as a time-dependent variable to minimize the effect of follow-up. Moreover, we performed sensitivity analyses with matching between exposed and non-exposed subjects and the results were very similar to those obtained in the main analysis. Finally, censoring women at the time of administration of another progestogen involved in meningioma risk (i.e., CPA and/or CMA) or due to pregnancy (period of high progesterone levels) also improves the reliability of the estimate of treatment risk.

This study, however, also had several limitations. First, The SNDS does not provide data on drug use before 2006. Thus, the impact of NOMAC exposure beyond 12 years was not studied. Intracranial irradiation is a risk factor for meningioma, and we cannot access this information before 2006. Radiation-induced meningiomas could occur up to 30 years after radiotherapy, usually due to underlying malignancy. However, we excluded women with a history of benign tumour and in a sensitivity analysis we excluded women for whom we had a record of history of malignant brain tumours, and for whom irradiation might have been indicated. This must have eliminated some cases in this situation and had very small impact on the results (RRa = 2.9 [2.4–3.7]). The SNDS lacks details on MRI and histology outcomes, including whether the meningiomas were ancient or recent, single or multiple. In addition, it does not specify how the meningiomas were discovered, although the referral for hospital treatment suggests they were symptomatic. If the meningioma is treated by simple monitoring or by radiotherapy (without surgery) in private practice, we cannot identify it in the SNDS and so underestimate the total number of meningiomas. However, meningiomas are rarely treated with radiotherapy alone, and even more rarely in the private sector (public care is required in most cases, especially for complex cases).[29] Moreover, this estimation error appears to be non-differential.

The therapeutic indications for NOMAC were unknown in this study. This is a limitation when assessing a drug's risk-benefit ratio. Nevertheless, the specialty of the initial prescriber—general practitioner or gynaecologist — had no influence on the risk of meningioma due to NOMAC, despite likely differences between the medical contexts. Indeed, for CPA, for which the therapeutic context was better defined, the specialty of the prescribing physician had no influence on meningioma risk.[6,20]

A further limitation was the non-inclusion of the Zoely® combined oral contraceptive pill (widely marketed in Europe Supplement 2), but not eligible for reimbursement in France and therefore not included in the SNDS), containing 2.5 mg NOMAC and 1.5 mg estradiol.

The first results of this study, available online following authorisation by a French scientific committee on progestins and risk of meningioma, had a considerable media impact in the French press for the general public in 2019.[30] After reviewing our results, the French National Medicine Agency (ANSM) sent information to healthcare professionals, warning of the risk of meningioma when using NOMAC.[31] At the ANSM's request, the Pharmacovigilance Committee (Prac) of the European Medicines Agency (EMA) then initiated a reassessment of the benefit/risk balance of nomegestrol-based products in 2021.[32] In addition, it recommended that nomegestrol-based products no longer be used for patients with a history of meningioma. NOMAC treatment requires mandatory regular monitoring for symptoms suggestive of meningioma during follow-up, and if a patient is diagnosed with a meningioma, treatment with these drugs should be permanently discontinued.

Following these recommendations, the European Commission asked EU member states, in a decision dated October 28, 2022, to modify the labelling authorization for medicines based on nomegestrol acetate.[32]

Consequently, the use of NOMAC in France in September 2023 had decreased by around 90% relative to September 2019. A more complete measurement of the impact of these regulatory measures is necessary.

### Conclusion

From 2007 to 2017, over 1,100,000 women in France started NOMAC treatment. We identified a strong association between NOMAC use and intracranial meningioma, for which the risk increases 12-fold after significant exposure (about 5 years of treatment at an effective dose). Further studies in various countries, notably in Europe, should also explore the risk of intracranial meningioma with all other progestogens marketed and used by cis-women, the only patients considered in this study, trans-women, and men over periods of several years.

All authors contributed with input on the design of the study and analytical plan, interpretation of results, writing of the first draft, and critical revision of the manuscript and analyses. All authors approved the submission. The corresponding author (NR) attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

### Data sharing statement

Under the terms of the SNDS data use agreement, the complete study data cannot be shared with other investigators (https://www.snds.gouv.fr). However, the authors try to share publication-related data as much as possible: algorithms and other additional information are provided in the supplemental data; aggregated data can be supplied upon request by contacting the authors at alain.weill@assurance-maladie.fr.

### Declaration of interests

We declare no financial relationships with any organizations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100928.

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