



## Indications leading to termination of pregnancy between 22+0 and 31+6 weeks of gestational age in France: A population-based cohort study

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**Indications leading to termination of pregnancy between 22<sup>+0</sup> and 31<sup>+6</sup> weeks of gestational age in France: a population-based cohort study**

Isabelle Monier,<sup>a, b</sup> Nathalie Lelong,<sup>a</sup> Pierre-Yves Ancel,<sup>a</sup> Alexandra Benachi,<sup>b</sup> Babak Khoshnood,<sup>a</sup> Jennifer Zeitlin,<sup>a</sup> Béatrice Blondel<sup>a</sup>

**Affiliations**

<sup>a</sup> Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes University, Paris, France.

<sup>b</sup> Antoine Beclere Maternity Unit, Department of Obstetrics and Gynaecology, University Paris Sud, AP-HP, Paris, France

**Corresponding Author**

Isabelle Monier

Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé)

Port Royal Maternity Unit, 53 Avenue de l'Observatoire, 75014 Paris, France

Tel: +33 (0)1 42 34 55 86

Fax: +33 (0)1 43 26 89 79

E-mail: [isabelle.monier@inserm.fr](mailto:isabelle.monier@inserm.fr)

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## Abstract

### Indications leading to termination of pregnancy between 22<sup>+0</sup> and 31<sup>+6</sup> weeks of gestational age in France: a population-based cohort study

Isabelle Monier, Nathalie Lelong, Pierre-Yves Ancel, Alexandra Benachi, Babak Khoshnood, Jennifer Zeitlin, Béatrice Blondel

**Objective:** To estimate the prevalence and indications of terminations of pregnancy (TOP) between 22<sup>+0</sup> and 31<sup>+6</sup> weeks of gestational age in France and to examine the characteristics of women by indication of TOP.

**Study design:** From the EPIPAGE 2 population-based cohort study of preterm births in France in 2011, we selected 5009 singleton live births, stillbirths and TOP that occurred between 22 and 31 weeks. We estimated the proportion of TOP by gestational age. We then classified terminations by indications into 4 categories: fetal anomalies (TOPFA), preterm premature rupture of the membranes (PPROM), maternal conditions and fetal growth restriction (FGR). We also classified TOPFA by type of anomaly. Maternal characteristics were compared between TOPFA and TOP for maternal or fetal conditions without congenital anomaly.

**Results:** 23.1% of all births and 54.3% of stillbirths were terminations. The proportion of terminations was 36.9% of all births at 22 weeks, 50.2% at 24 weeks and <10% at 30-31 weeks. 85.8% of terminations were for fetal anomaly, 4.4% for PPRM, 6.1% for maternal complications and 3.7% for severe FGR. Compared to women with a TOPFA, those with a termination for maternal or fetal conditions were more often nulliparous, single, African, obese, smokers and covered by non-standard insurance for women in socially deprived circumstances.

**Conclusion:** In France, there is a high proportion of TOP of which 14% are for indications other than congenital anomalies. Because rates of terminations have an impact on very preterm birth and perinatal mortality rates, studies on pregnancy outcome should report all terminations, not only those for congenital anomalies.

**Key-words:** terminations of pregnancy, preterm births, stillbirths, EPIPAGE 2

## Introduction

Terminations of pregnancy (TOP) are pregnancies that end to fetal deaths due to multiple conditions, most often congenital anomalies if the child is expected to have a risk of serious handicap, or pregnancy complications if there is substantial risk for the mother's life.(1) Most TOP are carried out at early gestational ages.(2,3) In some countries, terminations are also possible at later gestational age, after 21 completed weeks of gestational age (GA). These differences in policies and practices relating to TOP can affect estimates of perinatal mortality rates, if TOP are included in perinatal mortality statistics, and can influence evaluations of medical practices and survival of very preterm births.(4–7) A study on births between 22 and 31 weeks GA showed that more than 20% of stillbirths were TOP in many European regions and this proportion reached more than 40% in regions from Italy and France.(6) Therefore, information on the prevalence of TOP by gestational age and indication is important for international comparisons of perinatal health indicators. However, national-level data on TOP are scarce and most existing studies have focused on TOP for congenital anomalies,(8–13) whereas TOP are also carried out for other pregnancy complications.(14–16)

In a recent study, France reported the highest proportion of terminations among stillbirths at or after 22 weeks of gestation in Europe.(5) This study used aggregate data and was not able to describe the medical decision-making processes leading to the high number of TOP in France. Therefore, we aimed to estimate the prevalence of TOP among very preterm births, describe the indications of terminations and study the maternal characteristics according to the indication for termination using a population-based study of all births from 22 to 34 weeks GA in France in 2011.

## Methods

### *Study design and population*

The EPIPAGE 2 study is a national population-based prospective cohort of infants born between 22<sup>+0</sup> and 34<sup>+6</sup> weeks GA in 25 French regions in 2011 (N=7804).(17) All live births, stillbirths and TOP were included during three different periods according to gestational age at birth: 8 months for births between 22-26 weeks GA, 6 months for those between 27-31 weeks GA and 5 weeks for those between 32-34 weeks GA. The study population included 5009 singleton births between 22<sup>+0</sup> and 31<sup>+6</sup> weeks GA in 415 maternity units. Multiple pregnancies were excluded because the indications for TOP can differ from singleton pregnancies. We also excluded births between 32 and 34 weeks GA because of the short recruitment period for these births.

### *Variables*

Data were abstracted from medical charts using a standardized questionnaire. TOP were classified by medical indication into 4 exclusive and hierarchical classes: 1) fetal anomaly (TOPFA), 2) preterm premature rupture of the membranes (PPROM) defined as the rupture of membranes at least 12 hours before the beginning of labor, or anomaly of amniotic fluid, 3) maternal conditions including pregnancy complications related to diseases such as hypertensive and psychiatric disorders and 4) severe and isolated fetal growth restriction (FGR) with no hypertensive disorder and no apparent congenital anomaly.

We classified TOPFA according to the classification of multiple congenital anomaly (MCA) algorithm defined in the European Surveillance of Congenital Anomalies (EUROCAT) guidelines.(18) Congenital anomalies were classified into 8 exclusive groups following this order: 1) chromosomal anomalies, 2) genetic syndromes, 3) infections during pregnancy associated with fetal abnormalities (mainly toxoplasmosis and cytomegalovirus infections), 4) isolated neural tube defects, 5) isolated heart cardiac defects, 6) isolated renal disorders, 7) isolated other anomalies (eye, ear, face and neck anomalies, limb reduction defects, oro-facial clefts, digestive system, genital anomalies) and 8) potential multiple anomalies defined as two or more anomalies.(19) We created a ninth group for fetal anomalies with no information on the type of anomaly (or insufficient information on the type of anomaly to permit classification).

Maternal characteristics included maternal age, parity, family situation (cohabiting or single), country of birth, medical insurance, body mass index (BMI) before pregnancy and smoking during pregnancy. We used the type of medical insurance as an indicator of underprivileged situation: women have a non-standard insurance, if they are undocumented or have very low income.

#### *Prenatal care and management of terminations in France*

In France, an ultrasound is recommended at each trimester of pregnancy for women with no complication including an ultrasound screening for congenital anomalies between 22 and 24 weeks GA.(20) Terminations are allowed at any gestational age for congenital anomalies, medical conditions or social reasons if the continuation of the pregnancy would lead to risk for women's health or if the child is expected to

have a “serious illness, recognized as incurable at the time of diagnosis”.(1)  
Decisions for pregnancy terminations must be approved by a multidisciplinary  
committee for prenatal diagnosis.

#### *Statistical analysis*

We estimated the proportion of TOP with 95% confidence interval by gestational age,  
as a percentage of all births and as a percentage of stillbirths. For these calculations,  
all births included live births, TOP and spontaneous fetal deaths, and stillbirths  
included TOP and spontaneous fetal deaths. We also reported the proportion of  
feticides by gestational age. Then, we compared maternal characteristics between  
TOP for congenital anomalies and TOP for maternal conditions or FGR, using Chi  
square tests. Finally, we estimated the percentage of all TOPFA by type of fetal  
anomaly. In order to compare our results with other studies, we also reported the  
percentage of TOPFA between 22 and 26 weeks and between 27 and 31 weeks GA.

Percentage were weighted to account for the 9-week longer recruitment period for  
births at 22-26 weeks GA. Analyses were performed using STATA 13.0 software  
(StataCorpLP, College Station, TX, USA).

#### **Results**

Among the 5009 births between 22<sup>+0</sup> and 31<sup>+6</sup> weeks GA, there were 1266  
terminations (23.1%). (Table 1) The percentage of TOP was 36.9% (95% CI: 32.6-  
41.3) at 22 weeks; it increased to 50.2% (95% CI: 45.9-54.4) at 24 weeks GA and  
then decreased to less than 10% at 30-31 weeks GA. The percentage of TOP among  
stillbirths was 54.3% and it varied by gestational age from 35.9% to 70.4%. A feticide



was recorded in medical charts for 78.2% of terminations: 47.9% (95% CI: 40.5-55.5) at 22 weeks, 58.6% (95% CI: 51.7-65.1) at 23 weeks and more than 90% after 26 weeks. For instance, at 22 weeks GA, no mention of feticide was found for 48.8% of TOP for congenital anomalies, 60.9% of TOP for PPROM, 47% of TOP for maternal indications and 100% of TOP for severe FGR (n=4).

Table 2 presents the percentage of TOP by medical indication and gestational age. Overall, 85.8% of TOP were carried out for congenital anomaly, 4.4% for PPROM or anomaly of amniotic fluid, 6.1% for maternal complications and 3.7% for severe FGR. At 22-23 weeks GA, 78.4% of terminations were for congenital anomalies and this percentage increased with gestational age to 97.5% at 30-31 weeks GA. At these GA, the percentages of terminations for maternal conditions or FGR were 9.3% and 1.3% respectively. At 22 and 23 weeks of gestation, the 9 fetuses born after TOP carried out for isolated FGR had severe FGR with birthweight ranging between 110 and 350 grams.

Table 3 compared terminations for congenital anomaly to those for maternal indications or FGR. Women with terminations for maternal indications or FGR were often nulliparous (52.7% vs 40.8%,  $p=0.003$ ), single (11.8% vs 4.7%,  $p<0.001$ ), African (18.3% vs 7.6%,  $p<0.001$ ), obese (16.6% vs 9.8%,  $p=0.012$ ), smokers (22.9% vs 15.2%,  $p=0.011$ ) and covered by non-standard medical insurance for pregnant women in socially deprived circumstances (12.1% vs 7.5%,  $p=0.049$ ). No difference between the groups was found for maternal age.

Among TOP for fetal anomaly between 22 and 31 weeks, 22.6% (95% CI: 20.2-25.2) were for chromosomal abnormalities, 21.9% (95% CI: 19.5-24.5) for isolated neural tube defects, 13.8% (95% CI: 11.8-16.0) for isolated cardiac defects and 11.5% (95% CI: 9.7-13.6) for multiple anomalies. (Table 4) Among chromosomal anomalies, 44.2% were for Down's syndrome (Trisomy 21), 25.8% for Edward syndrome (Trisomy 18), 8.4% for Patau syndrome (Trisomy 13) and 21.6% for other chromosomal anomalies. Less than 10% of TOP for congenital anomaly were for genetic syndromes, infections or other isolated anomalies. These distributions were similar for TOPFA between 22 and 26 weeks and between 27 and 31 weeks GA.

## **Comment**

### *Main findings*

In France in 2011, terminations represented almost one quarter of all singleton births and half of stillbirths between 22 and 31 weeks GA. Most terminations were carried out for fetal anomaly, mainly for chromosomal abnormalities and isolated neural tube defects. About 15% of terminations were for maternal and fetal pregnancy complications unrelated to congenital anomalies but these indications were rare after 28 weeks GA. Women who had a termination for maternal or fetal pregnancy complications were more often nulliparous, obese, African, smokers and covered by non-standard medical insurance compared to those who had a termination for congenital anomaly.

### *Strengths and limitations*

The principal strength of our study is its population-based prospective design. We included all TOP between 22 and 31 weeks GA in 25 out of 26 French regions. The inclusion of all eligible births was ascertained by members of the regional coordinating committee in all maternity units.(17) Further, we included terminations for other reasons than congenital anomalies and we studied maternal characteristics related to these terminations, whereas most previous studies have focused only on terminations for congenital anomalies.(8–13)

Our study also has some limitations. We did not include terminations at 32-34 weeks GA because of the shorter recruitment period and consequently the small number of cases (N=15) and we did not have any information on terminations after 34 weeks. Additionally, there may be some classification errors: for instance spontaneous intrauterine deaths classified as TOP if scheduled TOP ended in fetal death before termination,(21) or conversely, some terminations being coded as stillbirths.

### *Interpretation*

We calculated that 23.1% of very preterm singleton births and 54.3% of stillbirths were terminations. These high proportions corroborate results from previous studies. For instance in 2003, in one French region, these proportions were 21.5% and 52.5% respectively whereas less than 6% of very preterm births were terminations in two regions in UK.(6) More generally, there is a high proportion of TOP regardless of gestational age in France, when compared to other European countries,(2) and this is especially true at low gestational ages.(5) Several factors contribute to this situation. France has an active policy of screening for congenital anomalies resulting in a high proportion of TOP among fetuses with congenital anomaly. For instance,

between 2002 and 2004, 96% and 98% of pregnancies diagnosed with a Down's syndrome and neural tube defects respectively ended in a termination.<sup>(7)</sup> In addition, terminations are allowed at any gestational age and this makes possible to wait for results of additional investigations to provide the best prognostic information to parents for their decision.<sup>(1)</sup> Finally, the second-trimester screening ultrasound is planned at 22-24 weeks, as opposed to before 20 weeks in many other countries, leading to a shift on the timing of terminations in France.

In our study, a feticide was not mentioned in medical charts for 48% of terminations at 22 weeks and 40% at 23 weeks of gestation. Some terminations without feticide may be explained because of absence of beating of fetal heart before the onset of labor or because some parents do not want a feticide. The information on the feticide may also have been forgotten in some medical files. In addition, there is no recommendation for feticide in France. This difference in medical guidelines may explain that no feticide was reported for 18% of terminations between 22 and 26 weeks in the EPICure study compared to 27.5% in our study.<sup>(21)</sup> Nevertheless, it seems that a feticide is routinely offered for terminations after 22 weeks GA in France.<sup>(22)</sup>

We found that women who had a termination for maternal or fetal compromise were different to those who had a termination for congenital anomaly. They were more often nulliparous, obese, African, with non-standard medical insurance and smokers. These characteristics are well-known risk factors for vascular diseases including pre-eclampsia and FGR.<sup>(23–25)</sup> We did not find any association with older maternal age which is known to be a major risk factor for hypertensive disorders during

pregnancy.(26) This result can be explained by the use of terminations for congenital anomaly as a comparison group, as older women also have an increased risk of having a fetus with a congenital anomaly.(27)

Chromosomal anomalies were the most frequent indication for terminations among all TOPFA (22.6%). Most of these anomalies were trisomies in our study as in UK(21) and more generally in Europe,(8) although there is an active policy of antenatal screening for Down's syndrome resulting in terminations before 22 weeks. We also found that isolated neural tube defects were a frequent indication. Between 22 and 26 weeks, 22.1% of terminations were carried out for isolated neural tube defects in our study and 31.2% in the EPICure study.(21) Several randomized controlled trials have demonstrated the efficacy of folic acid supplementation before pregnancy for the reduction of neural tube defects.(28) However, a population-based study showed that the prevalence of neural tube defects has not decreased in Europe during the last two decades.(29) This may be explained by difficulties in the implementation of folic acid supplementation, despite national recommendations issued in each country. In France, only 15% of pregnant women had folic acid before pregnancy in 2010.(30) In contrast, there was a decrease in the live birth prevalence of neural tube defects, as a result of prenatal diagnosis and terminations.(29)

In our study, we estimated that 15% of terminations were for maternal or fetal conditions. Maternal reasons were responsible of 6% of terminations. In 2003, 5% of terminations among very preterm births were for maternal reasons in one French region.(6) Two studies focusing on terminations for maternal conditions showed that maternal hypertensive disorders were the most frequent reason for these

terminations.(14,15) We also estimated that 3.7% of terminations were for severe isolated FGR. A study using the EPIPAGE 2 data showed that 11.6% of pregnancies suspected with early-onset FGR without a fetal anomaly resulted in terminations between 22 and 31 weeks and this proportion was higher when FGR was detected before 26 weeks of gestation.(31)

A high proportion of late terminations leads to increased preterm birth and stillbirth rates.(5,6,32) Less is known about the impact of late terminations on indicators of newborn and infant health, but some studies have shown an effect of policies and practices of terminations on mortality rates. Studies in Canada suggested that the increase in terminations for congenital anomaly between 2000 and 2010, especially at 20-21 weeks, led to a decrease in neonatal mortality rates and the prevalence of live-born infants with congenital anomalies.(4,12) Studies from countries where terminations are restricted also report higher rates of infant deaths associated with congenital anomalies.(6,33) These effects underscore the importance of taking into account regulations and medical practice regarding late terminations when comparing stillbirth and neonatal mortality rates between countries.

## **Conclusion**

Terminations of pregnancy between 22 and 31 weeks GA represent a high proportion of singleton very preterm births and stillbirths in France. The inclusion of all terminations in studies, not only those for congenital anomalies, is needed to understand medical practices, variations in preterm birth and stillbirth rates as well as infant health indicators in the perinatal period.

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349 Center for Epidemiology and Statistics Sorbonne Paris Cité, Département Hospitalo-  
350 Universitaire Risks in pregnancy, Paris Descartes University), Caroline Diguisto, MD,  
351 MSc (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research  
352 Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité,  
353 Département Hospitalo-Universitaire Risks in pregnancy, Paris Descartes University,  
354 Maternité Olympe de Gouges, University Francois Rabelais, Tours, France),  
355 Laurence Foix-L'Hélias, MD, PhD (Inserm UMR 1153, Obstetrical, Perinatal and  
356 Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and  
357 Statistics Sorbonne Paris Cité, Département Hospitalo-Universitaire Risks in  
358 pregnancy, Paris Descartes University, Sorbonne Universités, University Pierre and  
359 Marie CURIE Paris 06, Institut de Formation Doctorale, 4 Place Jussieu, 75252  
360 PARIS cedex 05, Paris, France, Department of Neonatal Pediatrics, Trousseau  
361 Hospital, AP-HP, Paris, France), Aurélie Garbi, MD (Department of Neonatology,  
362 Assistance Publique Hopitaux de Marseille, Marseille, France), Géraldine Gascoin,  
363 MD, PhD (Department of Neonatal Medicine, Angers University Hospital, Angers,  
364 France), Adrien Gaudineau, MD (Department of Obstetrics and Gynecology,  
365 Hautepierre Hospital, Strasbourg, France), Catherine Gire, MD (Department of  
366 Neonatology, North Hospital, Marseille, France), François Goffinet, MD, PhD (Inserm  
367 UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team  
368 (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, Département  
369 Hospitalo-Universitaire Risks in pregnancy, Paris Descartes University, Department  
370 of Obstetrics and Gynecology, Cochin, Broca, Hôtel Dieu Hospital, AP-HP, Paris,  
371 France), Gilles Kayem, MD, PhD (Inserm UMR 1153, Obstetrical, Perinatal and  
372 Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and  
373 Statistics Sorbonne Paris Cité, Département Hospitalo-Universitaire Risks in



374 pregnancy, Paris Descartes University, Sorbonne Universités, University Pierre and  
375 Marie CURIE Paris 06, Institut de Formation Doctorale, 4 Place Jussieu, 75252  
376 PARIS cedex 05, Paris, France, Department of Obstetrics and Gynecology,  
377 Trousseau Hospital, AP-HP, Paris, France), Bruno Langer, MD (Department of  
378 Obstetrics and Gynecology, Hautepierre Hospital, Strasbourg, France), Mathilde  
379 Letouzey, MD, MSc (Department of Neonatal Pediatrics, Poissy Saint Germain  
380 Hospital, France), Elsa Lorthe, RM, PhD (Inserm UMR 1153, Obstetrical, Perinatal  
381 and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and  
382 Statistics Sorbonne Paris Cité, Département Hospitalo-Universitaire Risks in  
383 pregnancy, Paris Descartes University), Emeline Maisonneuve, MD, MSc  
384 (Department of Obstetrics and Gynecology, Trousseau Hospital, APHP, Paris,  
385 France), Stéphane Marret, MD, PhD (Department of Neonatal Medicine, Rouen  
386 University Hospital and Région-INSERM (ERI 28), Normandy University, Rouen,  
387 France), Isabelle Monier, RM, PhD (Inserm UMR 1153, Obstetrical, Perinatal and  
388 Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and  
389 Statistics Sorbonne Paris Cité, Département Hospitalo-Universitaire Risks in  
390 pregnancy, Paris Descartes University), Andrei Morgan, MD, PhD (Inserm UMR  
391 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé),  
392 Center for Epidemiology and Statistics Sorbonne Paris Cité, Département Hospitalo-  
393 Universitaire Risks in pregnancy, Paris Descartes University), Jean-Christophe Rozé,  
394 MD, PhD (Department of Neonatal Medicine, Nantes University Hospital, Nantes,  
395 France, Epidémiologie Clinique, Centre d'Investigation Clinique (CIC004), Nantes  
396 University Hospital, Nantes, France), Thomas Schmitz, MD, PhD (Inserm UMR 1153,  
397 Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center  
398 for Epidemiology and Statistics Sorbonne Paris Cité, Département Hospitalo-

399 Universitaire Risks in pregnancy, Paris Descartes University, Department of  
400 Obstetrics and Gynecology, Robert Debré Hospital, Assistance Publique-Hôpitaux de  
401 Paris, Paris, France), Loïc Sentilhes, MD, PhD (Department of Obstetrics and  
402 Gynecology, Bordeaux University Hospital, Bordeaux, France), Damien Subtil, MD,  
403 PhD (Department of Obstetrics and Gynecology, Jeanne de Flandre Hospital, Lille,  
404 France), Héloïse Torchin, MD, MSc (Inserm UMR 1153, Obstetrical, Perinatal and  
405 Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and  
406 Statistics Sorbonne Paris Cité, Département Hospitalo-Universitaire Risks in  
407 pregnancy, Paris Descartes University, Neonatal Medicine and Resuscitation Service  
408 in Port-Royal, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris,  
409 France), Barthélémy Tosello, MD (Department of Neonatology, Assistance Publique  
410 Hôpitaux de Marseille, Marseille, France), Christophe Vayssière, MD, PhD  
411 (Department of Obstetrics and Gynecology, University Hospital, Toulouse, France,  
412 Research Unit on Perinatal Epidemiology, Childhood Disabilities and Adolescent  
413 Health, INSERM UMR 1027, Paul Sabatier University, Toulouse, France), Norbert  
414 Winer, MD, PhD (Department of Obstetrics and Gynecology, University Hospital,  
415 INRA, UMR 1280 Physiologie des adaptations nutritionnelles, Nantes, France),  
416 Jennifer Zeitlin (Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology  
417 Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris  
418 Cité, Département Hospitalo-Universitaire Risks in pregnancy, Paris Descartes  
419 University).

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## 425 **Disclosure of interests**

426 The authors report no conflict of interest

427

## 428 **Authorship**

429 IM, JZ and BB analysed the data and drafted the manuscript. NL, AB, BK and PYA  
430 participated in the interpretation of the results and made suggestions for revisions.

431 PYA contributed to the design of the study.

432

## 433 **Details of ethics approval**

434 Ethics approval was received from the National Data Protection Authority (CNIL no.  
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