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ARTICLE

Living in a low socioeconomic status neighbourhood is associated with lower cumulative ongoing pregnancy rate after IVF treatment

BIOGRAPHY

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KEY MESSAGE

Low neighbourhood socioeconomic status (SES) is associated with reduced odds of achieving an ongoing pregnancy within 2.5 years of IVF treatment compared with high neighbourhood SES. This underscores that, even when fertility care access is equitable, individuals residing in a low SES neighbourhood face disadvantages.

ABSTRACT

Research question: Does an association exist between neighbourhood socioeconomic status (SES) and the cumulative rate of ongoing pregnancies after 2.5 years of IVF treatment?

Design: A retrospective observational study involving 2669 couples who underwent IVF or IVF and intracytoplasmic sperm injection treatment between 2006 and 2020. Neighbourhood SES for each couple was determined based on their residential postal code. Subsequently, SES was categorized into low (<p20), medium (p20–p80), and high (>p80). Multivariable binary logistic regression analyses were conducted, with the cumulative ongoing pregnancy within 2.5 years as the outcome variable. The SES category (reference category: high), female age (reference category: 32–36 years), body mass index (reference category: 23–25 kg/m^2), smoking status (yes/no), number of oocytes after the first ovarian stimulation, embryos usable for transfer or cryopreservation after the first cycle, duration of subfertility before treatment and insemination type were used as covariates.

Results: A variation in ongoing pregnancy rates was observed among SES groups after the first fresh embryo transfer. No difference was found in the median number of IVF treatment cycles carried out. The cumulative ongoing pregnancy rates differed

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significantly between SES groups (low: 44%; medium: 51%; high: 56%; $P < 0.001$). Low neighbourhood SES was associated with significantly lower odds for achieving an ongoing pregnancy within 2.5 years (OR 0.66, 95% CI 0.52 to 0.84, $P < 0.001$).

Conclusion: Low neighbourhood SES compared with high neighbourhood SES is associated with reducing odds of achieving an ongoing pregnancy within 2.5 years of IVF treatment.

INTRODUCTION

Subfertility is defined as the inability to achieve a clinical pregnancy after 12 months of regular unprotected intercourse (*Zegers-Hochschild et al., 2009*). IVF is a well-established treatment for subfertility. Subfertility is experienced by one in six couples, making it a substantial public health concern (*Boivin et al., 2007*). Despite years of research and experience in the field of IVF, relatively modest results have been reported, with a global reported pregnancy rate of 34.6% after embryo transfer (*Wyns et al., 2021*).

Alongside established factors affecting subfertility and IVF outcomes, such as female age and body mass index (BMI) (*Rittenberg et al., 2011*), interest in exploring the potential influence of socioeconomic status (SES) is growing (*Imrie et al., 2021*). It has been suggested that lifestyle factors can affect subfertility and the success rate of IVF (*Rooney and Domar, 2014*). Within published research, variables such as educational attainment, occupation and ethnic background are often used either individually or collectively as indicators for SES (*Imrie et al., 2021*). This categorization allows for a better understanding of the profile of subfertile patients and provides a framework for investigating its potential effect on IVF outcomes.

One approach to characterize the SES of a subfertile patient is by using Neighbourhood SES, which classifies patients based on the average SES factors of their residential neighbourhoods (*CBS-Netherlands, 2016*). This can be used as an indicator for the living environment and conditions (*Burgos Ochoa et al.,2021*). Low neighbourhood SES exerts a detrimental effect on overall health and wellbeing, a phenomenon evident during pregnancy and in the initial stages of life. It is shown that maternal and perinatal mortality and morbidity are associated with neighbourhood SES (*de Graaf et al., 2013*; *Bertens et al., 2020*; *Burgos Ochoa et al., 2021*). Additionally, suboptimal fetal growth and development are associated with low SES (*Silva et al., 2010*; *Ball et al., 2013*; *Gootjes et al., 2019*; *Lu et al., 2021*). Moreover, specific adverse pregnancy outcomes, such as spontaneous miscarriage, preeclampsia, preterm delivery, large for gestational age infants, low birth weight, caesarean delivery and obstetrical haemorrhage, have been reported more frequently in woman with a low individual SES (*Silva et al., 2008*; *Kim et al., 2018*; *Amjad et al., 2019*, *Keenan-Devlin et al., 2022*).

The possible association between SES and IVF outcomes has received limited attention. A systematic review identified six studies specifically addressing the potential effects of SES on fertility treatment outcome (*Imrie et al., 2021*). Recent investigations have produced findings that contradict any substantial influence of SES on IVF outcomes (*Liu et al., 2021*; *Veira et al., 2022*). Nevertheless, an independent role for ethnicity in determining IVF and intracytoplasmic sperm injection success was suggested by two studies (*Patel et al., 2016*; *Andre et al., 2023*). Another recent study reported a higher risk of spontaneous miscarriage outcomes among pregnancies after embryo transfer for unemployed woman and couples living in non-capital areas (*Kim et al., 2023*). In addition, a large study showed that, among socioeconomically advantaged women in high-income countries, all forms of medically assisted reproduction (MAR) more commonly result in live births (*Goisis et al., 2023*).

IVF treatment can be considered costly; therefore, financial resources may account for some of the found differences in IVF outcomes between SES categories. Since the start of IVF treatment in the Netherlands, however, three cycles of IVF treatment have been reimbursed by the mandatory health insurance. This enables every couple to partake in IVF treatment, irrespective of their ability to pay for it. This makes the Netherlands a unique setting to further study the association between SES and IVF outcomes. Therefore, our aim was to investigate the association between neighbourhood SES and cumulative ongoing pregnancy within 2.5 years after the first IVF treatment. Neighbourhood SES was categorized into high (>p80), medium (p20–p80) and low SES (<p20) groups for analysis.

MATERIALS AND METHODS

Study design, participants and setting

In this retrospective cohort study, clinical data from IVF treatments carried out between 2006 and 2020 at the IVF centre of Erasmus MC, University Medical Centre, Rotterdam, were used (FIGURE 1). Individual electronic patient records were used for data on fertility treatments. Neighbourhood SES was used as an indicator for living environment and conditions of the couples undergoing IVF treatment.

Neighbourhood SES scores are calculated by the Netherlands Institute for Social Research (*CBS-Netherlands, 2016*) per four digit postal-code area (comprising around 4000 inhabitants or covering an area of approximately 5.3 km^2). These scores are based on household income, type of employment and educational attainment (*CBS-Netherlands, 2016*; *Burgos Ochoa et al., 2021*). The SES scores were grouped into quintiles, and categorized as follows: low SES (first quintile of neighbourhood SES score), medium SES (second to fourth quintile of neighbourhood SES score) and high SES (fifth quintile of neighbourhood SES score). These neighbourhood SES scores are updated and published every 4 years, and the SES score published closest to the start date of the couple's first IVF cycle was used.

It is worth noting that some couples might have changed residences during their treatment, potentially exposing them to different levels of neighbourhood SES. Unfortunately, these couples could not be identified, as only the most recent postal code was available to us. Research has shown that people typically move within a similar area (*Bilal et al., 2019*). In a previous study using the same neighbourhood SES data, a sensitivity analysis was conducted, omitting individuals who had moved, and it revealed no effect on the results (*Burgos Ochoa et al.,2021*). Therefore, the results of our study are unlikely to be influenced

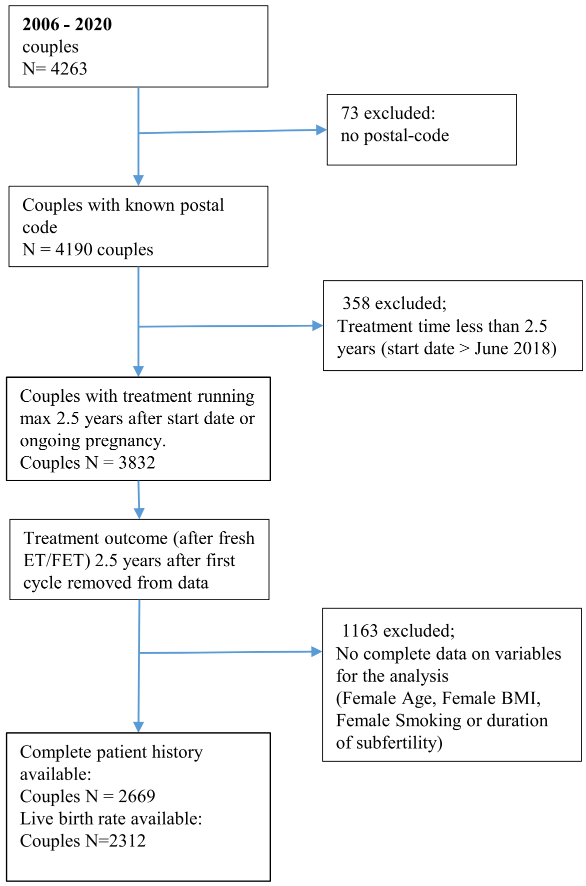

FIGURE 1 Included and excluded cycles. BMI, body mass index; ET, embryo transfer; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection.

by patients who relocated to another SES area during the study period.

At the start of IVF treatment, information about smoking, BMI and subfertility was registered in the patient file by the gynaecologist. Treatment outcomes were proactively collected by health professionals to minimize the risk of under-reporting. Therefore, missing data are more likely to be linked to the responsible physician than to SES category.

IVF procedure

Women underwent routine ovarian stimulation using either a gonadotrophin-releasing hormone agonist or antagonist co-treatment protocol with recombinant FSH: Puregon (Organon, Oss, the Netherlands); Gonal-F (Merck Serono, Aubonne, Switzerland); Menupur (Ferring, St Prex, Switzerland); Bemfola (Gedeon Richter, Dilbeek, Belgium); or Rekovelle® (Ferring, St Prex, Switzerland) (*Eijkemans et al., 2006*; *Nyboe Andersen et al., 2017*) or highly purified urinary FSH (Menopur, Ferring, St Prex, Switzerland). The final follicular maturation was triggered using human recombinant HCG: Ovitrelle® (Merck Serono, Aubonne Switzerland); Pregnyl® (Organon, Oss, the Netherlands) or decapeptyl (Ferring, Parsippany, NJ, USA). After oocyte retrieval, IVF was carried out at the IVF laboratory of the Erasmus MC, University Medical Centre, Rotterdam. Standardized procedures were followed for the insemination of oocytes and embryo culture, as previously described (*van Marion et al., 2022*). Embryo selection for fresh transfer and cryopreservation was based on morphological assessment (*Alpha Scientists in Reproductive and Embryology, 2011*; *van Marion et al., 2021*). Single embryo transfer (SET) was the standard practice with the possibility of double embryo transfer (DET) (13.7% DET in the first cycle, with a declining trend from 2006 (29.4%) to 2018 (10.5%).

For this study, consecutive fresh and frozen embryo transfers resulting from a single ovarian stimulation were defined as one IVF cycle. Multiple IVF cycles within their IVF treatment could be undergone by couples.

Outcome variable

The primary outcome variable, cumulative ongoing pregnancy, was defined as the first ongoing pregnancy resulting from consecutive cycles within a maximum time frame of 2.5 years after the start of the first IVF cycle. Ongoing pregnancy was confirmed by a detected fetal heartbeat on ultrasound at 12 weeks of gestation. Couples with a confirmed ongoing pregnancy were censored from the dataset if they had undergone a subsequent IVF cycle or frozen embryo transfer.

A 1-year period is sufficient for assessing cumulative pregnancy rates (*Collins et al., 1995*; *Taylor, 2003*); however, a substantial number of couples had extended intervals without treatment for reasons unrelated to medical factors. After 1 year, 32% of the non-pregnant group remained in treatment, and this proportion decreased to 9.4% after 2.5 years. Therefore, a 2.5-year duration was chosen to determine the cumulative ongoing pregnancy rate within the database.

Live birth rates were not available for all treatments and were not considered as main outcome. They were, however, used in an additional analysis involving a subset of the data ($n = 2312$ couples). Maternal age, body mass index (BMI) and smoking status are potential confounding factors affecting the exposure and outcome variables, so they were added as covariates in the multivariable binary logistic regression model. Other covariates included the number of oocytes retrieved after the initial ovarian stimulation, the number of embryos suitable for transfer or cryopreservation after the first cycle, the insemination method (IVF or ICSI), and the duration of subfertility before treatment. These factors are likely to influence the success of IVF treatment and, consequently, the outcome variable; however, they cannot be considered confounders as their association with the exposure, e.g. neighbourhood SES, has not been researched and is not present in the dataset. Couples with incomplete or incorrect data on any of these covariates were excluded.

Female age and BMI were initially reported as continuous variables but were included in the model as categorical variables. Body mass index was rounded up to two decimal places. Smoking status, originally reported as the number of cigarettes smoked per day, was coded as either smoking (yes) or non-smoking (no).

In descriptive analyses, results from the first cycle were presented per SES group, including fertilization rate (rate of normally fertilized zygotes/oocyte retrieved), sperm concentration, motile sperm count (defined as the concentration progressive motile sperm cells x semen volume), number of oocytes obtained after the first ovarian stimulation, number of embryos usable for embryo transfer or cryopreservation, biochemical pregnancy after the first fresh transfer (defined as a positive urinary β-HCG test 10–12 days after the embryo transfer) and ongoing pregnancy after the first fresh transfer (defined as a fetal heartbeat on ultrasound at 12 weeks of gestation).

Missing data

From the entire dataset of couples (n = 4263), some were excluded from the analysis (FIGURE 1). First, 73 couples without a known postal code were excluded (1.7%). Next, couples with a first cycle after June 2018 were also excluded (n = 358 [8.4%]) to ensure that every couple had sufficient time to complete 2.5 years of treatment within the study period. Finally, couples with incomplete data on the variables were excluded (n = 1163 [27%]). This resulted in 2669 couples with complete data for our analysis. For the repeated analysis involving live births, an additional 357 couples were excluded owing to missing data on the outcome variable.

Individual SES characteristics, such as education and ethnicity, were only available in a limited sample. The main infertility diagnosis was not available in the data. Therefore, these variables could not be included in any analysis.

Statistical analysis

Baseline data were presented using descriptive analyses, including mean and SD or median and interquartile range for continuous variables, and number and percentages for categorical data. Continuous data were compared using a Mann–Whitney U test. Chi-squared test and Fisher's exact test were used to analyse the categorical data. Multivariable binary logistic regression analysis was conducted with cumulative ongoing pregnancy as outcome variable and SES categories as the main determinant. High SES served as reference category. In addition to SES categories, potential confounders included female age, female BMI, number of oocytes after the first ovarian stimulation, usable embryos after the first cycle, duration of subfertility before treatment, insemination method (IVF or ICSI) and female smoking. Female age and female BMI had a non-linear relationship with the outcome, particularly in the lower and upper ends of the distribution. Therefore, they were included as categorical covariates. The chosen BMI categories are narrower than that typically used, but they were selected to better represent the variation present in our data (BMI category: <22, 23–25, 26–28, >29) with BMI category 23–25 as a reference category. For age, the categories were defined as younger than 31 years, 32–36 years and older than 37 years, with the age group 32–36 years as the reference category.

Only couples with complete data for the variables in the model were included in this analysis.

In addition, the analysis was repeated in a subset of the data (n = 2312 couples), with cumulative live birth as the outcome variable. IBM SPSS Statistics 28.0.1.0. software (IBM, Almonk, NY, USA) was used for statistical analyses.

Ethical approval

The Medical Ethical Committee of the Erasmus MC examined the study protocol and issued a waiver for the Medical Research Act (MEC-2022-0434, dated 15 July 2022), so no formal consent was needed.

RESULTS

Participants

Between 2006 and 2020, a total of 4263 couples underwent IVF or IVF/ICSI treatment. A total of 2669 couples with complete postal-code information and patient characteristics (female age, BMI, smoking status and duration of subfertility) were included. These couples had all undergone treatment for up to 2.5 years (FIGURE 1). Throughout this period, the ratio between high and low SES couples remained stable, with about 23% of couples residing in low SES neighbourhoods. Baseline characteristics of the included treatments are presented in TABLE 1. Female BMI, female smoking and the duration of subfertility were significantly higher in the low neighbourhood SES group ($P < 0.001$, $P = 0.01$ and $P < 0.001$, respectively). Sperm parameters did not differ between SES groups, as well as the median number of started IVF cycles (TABLE 2).

Treatment outcome after the first cycle

After the first fresh IVF cycle, no significant differences were observed in fertilization rate, the number of embryos available for fresh transfer or cryopreservation after the first cycle, biochemical pregnancy, or miscarriages among the three SES groups. A small difference was noted in the mean number of oocytes retrieved (low SES: 8.42 ± 0.14; high SES: 8.58 ± 1.33; $P = 0.03$, pairwise value for low vs high).

TABLE 1 BASELINE CHARACTERISTICS OF INCLUDED COUPLES

Start of treatment	SES low	SES medium	SES high	Total	*P*-value
Total included	632 (23.7)	1434 (53.7)	603 (22.6)	2669 (100)	
Female age, years	34.1 (± 5.2)	33.9 (± 5.0)	34.1 (± 4.7)	34.0 (± 5.0)	0.56
Female body mass index, kg/m^2	24.8 (± 4.5)	24.2 (± 4.2)	23.8 (± 3.9)	24.3 (± 4.2)	<0.001
Female smoking	164 (25.9 %)	319 (22.2)	113 (18.7)	596 (22.0)	0.01
Duration of subfertility, months	47 (24–60)	41 (23–51)	39 (23–49)	42 (23–53)	<0.001

Each treatment is derived from a unique patient couple.

Data are presented as number (%), mean (± SD) or median (interquartile range). Continuous data were compared using a Mann–Whitney U test. Chi-squared test and Fisher's exact test were used to analyse the categorical data.

SES, socioeconomic status.

TABLE 2 OUTCOME CHARACTERISTICS OF THE FIRST IVF CYCLE AND CUMULATIVE OUTCOME AFTER 2.5 YEARS OF TREATMENT

Characteristics	SES low	SES medium	SES high	Total	*P*-value
Total included	632 (23.7)	1434 (53.7)	603 (22.6)	2669 (100)	
Started cycles per treatment	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	0.23
Sperm concentration in ejaculate during first cycle, 10^6/ml					
IVF	45 (23–75)	44 (24–75)	50 (26–81)	45 (24–77)	0.22
ICSI	2.3 (0.7–10)	2.0 (0.4–7.4)	2.0 (0.4–8.0)	2.1 (0.4–8.0)	0.21
Motile sperm count in ejaculate (VCM) during first cycle					
IVF	58 (29–120)	63 (26–125)	64 (25–140)	60 (27–126)	0.67
ICSI	1.2 (0.2–4)	0.9 (0.1–4)	0.5 (0.1–3)	0.5 (0.1–3)	0.18
Number of oocytes retrieved after first ovarian stimulation	7 (4–11)	7 (4–11)	7 (4–11)	7(4–11)	0.03
Fertilization rate of first cycle (number 2PN per oocyte), %					0.64
0–25	93 (17.7)	230(19.4)	106 (20.4)	429 (19.2)	
25–50	151 (28.8)	309(26.1)	125 (24.1)	585 (26.3)	
50–75	157 (30.0)	369(31.2)	155 (29.9)	681 (30.6)	
75–100	123 (23.5)	275(23.2)	132 (25.5)	530 (23.8)	
Number of embryos (for embryo transfer or cryopreservation after the first cycle)	1 (0–3)	1(0–3)	1 (1–3)	1 (0–3)	0.19
Biochemical pregnancy (HCG) first cycle (fresh embryo transfer)					
Yes	150 (23.7)	360 (25.1)	164 (27.2)	674 (25.3)	0.08
Ongoing pregnancy first cycle					
Yes	108 (17.1)	262 (18.3)	126 (20.9)	496 (18.6)	0.03
12-week pregnancy loss first cycle					
Yes	42 (28.0)	98 (27.2)	38 (23.2)	178 (26.4)	0.51
Cumulative ongoing pregnancy within 2.5 years					
Yes	275 (43.5)	734 (51.2)	337 (55.9)	1346 (50.4)	<0.001
Cumulative live birth rate within 2.5 years	194 (36.5)	560 (44.6)	267 (50.8)	1021 (44.2)	<0.001
Missing	101 (16.0)	179 (12.5)	77 (12.8)	357 (13.4)	

Each treatment is derived from a unique patient couple.

Data are presented as number (%) or median (interquartile range). Mann–Whitney U test was used to compare continuous data. Chi-squared test and Fisher's exact test were used to analyse categorical data.

ICSI, intracytoplasmic sperm injection; SES, socioeconomic status; VCM, volume–concentration–motility (amount of progressive motile sperm in whole ejaculate); 2PN, two pronuclei.

Also, the ongoing pregnancy outcome (low SES: 17%; medium SES: 18%; high SES: 21%; $P = 0.03$) varied between the SES groups (TABLE 2).

Cumulative treatment outcome

The cumulative ongoing pregnancy rate had significant variations among the three SES groups (SES low 44% versus SES medium 51% versus SES high 56%; $P < 0.001$).

The main analysis showed a significantly lower odds ratio for cumulative ongoing pregnancy for the low SES groups (OR 0.66, 95% CI 0.52 to 0.84, $P < 0.001$) compared with the high SES group. Notably, the inverse association of cumulative ongoing pregnancy rate with low SES was independent of the covariates female age, BMI and smoking and the number of oocytes after the first ovarian stimulation or number of embryos transferred or cryopreserved after the first cycle, duration of subfertility and insemination method (TABLE 3).

Additional analysis with cumulative live birth rates as outcome ($n = 2312$ couples) consistently demonstrated a significant association ($P < 0.001$) between low neighbourhood SES and lower live birth rate (TABLE 4). Missing data for live birth was slightly higher for the low neighbourhood SES group (low SES 16%, high SES 13%)

DISCUSSION

The study findings suggest that residing in low SES neighbourhoods is associated with a reduced likelihood of achieving an ongoing pregnancy within 2.5 years after starting IVF treatment. Furthermore, this association extends to live birth rates, as demonstrated in a subset of patients.

Existing research on the association between SES in general and IVF outcome has yielded conflicting results. Two recent studies (*Liu et al., 2021*; *Veira et al., 2022*) found no effect of SES on ongoing pregnancy rates, whereas a systematic review on the topic revealed contradictory findings among individual studies (*Imrie et*

TABLE 3 OUTCOME OF THE MULTIVARIABLE BINARY LOGISTIC REGRESSION ANALYSIS IN 2669 COUPLES, WITH CUMULATIVE ONGOING PREGNANCY AS THE OUTCOME VARIABLE AND SOCIOECONOMIC STATUS CATEGORIES AS MAIN DETERMINANT

			95% CI for OR	
Variable	**OR**	***P*-Value**	**Lower**	**Upper**
SES				
High	Reference			
Low	0.66	<0.001	0.52	0.84
Medium	0.87	0.18	0.71	1.07
Female age, years				
32–36	Reference			
<31	1.14	0.19	0.94	1.40
>37	0.43	<0.001	0.35	0.53
Female BMI, years				
23–25	Reference			
<22	1.18	0.11	0.96	1.44
26–28	0.87	0.27	0.67	1.12
>29	0.73	0.02	0.57	0.94
Female smoking	0.79	0.02	0.65	0.96
Duration of subfertility, quartile	Reference			
2	0.99	0.98	0.79	1.25
3	1.03	0.80	0.82	1.30
4	0.85	0.18	0.68	1.08
Number of oocytes (first stimulation)	1.07	0.44	0.99	1.03
Number of embryos used for embryo transfer/ cryopreservation (first cycle)	1.23	<0.001	1.17	1.30
Insemination method (ICSI/IVF)	1.25	0.01	1.05	1.49

Female age, female BMI, female smoking, duration of infertility, number of oocytes after the first ovarian stimulation, number of usable embryos after the first cycle and fertilization method were included as potential confounders.

$P < 0.05$ was considered significant.

BMI, body mass index; ICSI, intracytoplasmic sperm injection; SES, socioeconomic status.

al., 2021). In the present study, a difference in ongoing pregnancies between the neighbourhood SES groups was found after the first cycle. When using cumulative ongoing pregnancy within a time frame of 2.5 years, the disparities became more pronounced. Research shows that, in both fertile and subfertile populations, conception can take up to several months or longer (Collins et al., 1995; Taylor, 2003; Garrido et al., 2011). Furthermore, cumulative IVF outcomes are the preferred measures when reporting on IVF success (Tiitinen et al., 2004; Maheshwari et al., 2015; Rienzi et al., 2021). Altogether, in our view, pregnancy outcomes should be assessed after a longer period instead of just looking at one cycle. Conflicting results with earlier studies might be explained by the different approach. This approach showed that the association between neighbourhood SES and IVF outcome becomes clearer when using cumulative IVF outcomes.

Financial status is frequently cited as a contributory factor to diminished MAR, and specifically IVF treatment outcomes within low SES groups, with the assumption that couples with low financial status may not be able to afford as many IVF cycles (Chambers et al., 2014). A recently published study has challenged this assumption by revealing that household income and IVF insurance coverage are not associated with pregnancy, pregnancy loss or live birth (Chung et al., 2022). In the present study, the financial argument is essentially non-existent because, in the Netherlands, health insurance is mandatory, and this insurance includes the reimbursement of three IVF cycles for every patient. In the present study, we found no difference in the average number of cycles completed within 2.5 years between the different SES groups. A small portion (7.4%) of our patients, however, continued treatment after the last reimbursed treatment. When reanalysing our data with only reimbursed cycles, the odds ratio is similar (data not shown), confirming that the number of IVF cycles had no effect on the association found. Altogether, this implies that financial barriers to IVF access are less likely to explain the observed differences in outcome in the present study.

Financial status, however, may indirectly affect lifestyle behaviours that affect health. Lifestyle involves health risk behaviours, such as smoking and alcohol consumption, and also health promoting behaviours, such as physical exercise, eating healthy food and stress management (Walker et al., 1987; Pronk et al., 2004; Morawa and Erim, 2018). The range of possible choices can be determined by an individual's SES status (Cockerham, 2010; Cockerham WC, 2016). In the present study, only smoking as a health risk behaviour and BMI as a proxy of health risk behaviour could be included. Both were significantly higher for the low SES group. Our analyses, however, showed that the association of neighbourhood SES and IVF outcome persisted independent of female BMI, smoking and age. We cannot rule out that lifestyle factors have influenced our observations, as we only had information about smoking status and BMI.

The duration of subfertility is a known factor influencing pregnancy chance (van Loendersloot et al., 2010). A longer pre-treatment time might allow selection of a more severe subfertile population. It was found in this study that a longer duration of subfertility did not significantly affect the odds ratios of low neighbourhood SES on cumulative ongoing pregnancy. Interestingly, a significantly longer duration of subfertility was observed in the low SES group compared with the high SES group. This suggests that, even with equal financial access to reproductive care, patients within the low SES group may experience a delay in starting their treatment. This delay could be due to other life stressors or a lack of awareness about fertility and available treatment options.

Mechanisms explaining the association between neighbourhood SES and IVF outcomes are likely multifactorial. One

TABLE 4 OUTCOME OF MULTIVARIABLE BINARY LOGISTIC REGRESSION ANALYSIS OF 2312 COUPLES, WITH CUMULATIVE LIVE BIRTH AS THE OUTCOME VARIABLE AND SOCIOECONOMIC CATEGORIES AS MAIN DETERMINANT

			95% CI for OR	
Variable	**OR**	***P*-value**	**Lower**	**Upper**
SES				
High	Reference			
Low	0.63	<0.001	0.48	0.82
Medium	0.81	0.74	0.66	1.02
Female age, years				
32–36	Reference			
<31	1.22	0.07	0.98	1.51
>37	0.39	<0.001	0.31	0.49
Female BMI, years				
23–25	Reference			
<22	1.17	0.15	0.95	1.46
26–28	0.74	0.04	0.56	0.98
>29	0.65	0.03	0.49	0.87
Female smoking	0.70	0.001	0.56	0.87
Duration of subfertility, quartile	Reference			
2	1.00	0.98	0.78	1.28
3	0.94	0.94	0.73	1.21
4	0.73	0.02	0.57	0.95
Number of oocytes (first stimulation)	1.00	0.87	0.98	1.02
Number of embryos used for embryo transfer/cryopreservation (first cycle)	1.22	<0.001	1.16	1.29
Insemination method (ICSI/IVF)	1.33	0.003	1.10	1.61

Female age, female body mass index (BMI), female smoking, duration of subfertility, number of oocytes after the first ovarian stimulation, number of usable embryos after the first cycle and fertilization method were included as potential confounders.

$P < 0.05$ was considered significant.

ICSI, intracytoplasmic sperm injection; SES, socioeconomic status.

explanation may be offered by chronic exposure to negative environmental factors. Individuals in a low SES environment may experience higher levels of perceived stress (Algren et al., 2018). Numerous stress factors are known to affect health, i.e. overcrowding, noise pollution, bad housing quality and high crime rates, which affects mental and physical health (Middleton, 1998; Fabio et al., 2011; Barbaresco et al., 2019; Nkosi et al. 2019; Singh et al., 2019). An effect of stress on implantation has been reported (deCatanzaro, 2011); however, our data do not directly support this. Several studies have reported a lower pregnancy rate in patients with higher stress levels (Smeenk et al., 2005; Turner et al., 2013; Aimagambetova et al., 2020). There are indications that social stress during the prenatal period and in childhood results in higher inflammation in later life (Pedersen et al., 2018). Pollution is another negative environmental factor that can affect health and pregnancy outcomes. An association between industrial air pollution and health in general, and more specifically pregnancy, is reported (Frutos et al., 2015; Choe et al., 2018; Gaskins et al., 2019; Bergstra et al., 2022). Certain low SES communities experience worse air pollution (Hajat et al., 2015). The Rotterdam area has a big industrial area (Europoort), and air pollution is not evenly distributed (Bergstra et al., 2018; Arcadis, 2022). Chronic exposure to stressors and pollution in early life may lead to epigenetic changes that affect biological responses in adulthood (Lam et al., 2012).

Proximity to the fertility clinic may be a factor affecting the likelihood of undergoing MAR treatment (Lazzari et al., 2022). Whether this affects the low SES group in the present study, and therefore our results, is unclear. It is known, however, that low SES neighbourhoods are more often in urbanized areas, which are closer to hospitals.

Most research into differences in IVF outcome (and also pregnancy) focus on maternal characteristics. Paternal characteristics, however, do also play a role, and this could be true for the association between SES and IVF outcome. Altered epigenetics in spermatozoa might play a role in the lower IVF success rate we found in the low SES group. Accumulating evidence suggests that environmental factors can influence epigenetics in spermatozoa (Donkin and Barres, 2018). There are indications that sperm RNA transmits environmental information to the offspring (Vojtech et al., 2014; Zhang et al., 2019). It remains unclear, however, if this RNA plays and role during early embryo development after fertilization, and, if so, what kind of role this RNA plays.

Second, chronic high overall stress might affect oocyte quality and, therefore, IVF success rate. Some small studies suggest a negative effect of low SES or individual level exposures, such as ethnicity, on ovarian reserve (Iglesias et al., 2014; Barut et al., 2016; Bleil et al., 2018). In addition, low SES is found to be associated with earlier menopause (Gold et al., 2001; Castelo-Branco et al., 2005; Kapur et al., 2009; Velez et al., 2010; Richardson et al., 2014). A systematic review on the association between educational level and age at menopause found no conclusive evidence, only a weak association between lower educational level and earlier age of menopause (Canavez et al., 2011). If oocytes of women exposed to low SES circumstances are affected by stress, this might manifest itself in oocyte quality. Interestingly, however, we did not find any significant differences in fertilization rate or embryo usage rate between the SES groups.

The large number of couples with known treatment outcome is a major strength of this study. During the long study period, the patient characteristics remained stable, and the neighbourhood SES was recalculated every 4 years. Furthermore, we adapted a longitudinal approach over a long study period between 2006 and 2020, making it possible to analyse cumulative treatment outcomes instead of only first cycle treatment outcomes. Furthermore, SES neighbourhood scores are dynamic and may change over time. This was considered by using the most recently published score for each individual IVF cycle. Another major strength is that the design of the Dutch health system excludes the financial health seeking bias from our study in contrast to earlier published studies.

One limitation of our study is that data on smoking, BMI, duration of subfertility and live birth rate were not available for all couples. We were still able to include 2669 couples with complete data in a multivariable binary logistic regression analysis on cumulative ongoing pregnancy. A difference in missing data on live births was seen between the high SES and low SES group. This may give a small bias in our secondary outcome. As the treating physician was responsible for the collection of these data, it is unlikely that these differences result from selection bias by SES. Another limitation is that pregnant couples that conceived naturally could be unjustly labelled as not pregnant in our data. In our clinic, an IVF treatment starts on average at 3.5 years of subfertility (TABLE 1) and is often preceded by intrauterine insemination. Therefore, the chances of naturally conceived pregnancies are expected to be small and may account for a small proportion of our data. Unfortunately, additional analysis on individual characteristics, such as educational level, ethnicity, main infertility diagnosis or language proficiency could not be conducted owing to a lack of data. This study covers 14 years of IVF data, and IVF results may have improved over this period. To investigate the effect of changes over time, we separately analysed the data for 2014–2018 and 2006–2013, and found similar odds ratios for both time periods compared with the whole cohort (results not shown). Last, our study findings have low generalizability to countries that have other policies and facilities regarding IVF treatment.

As the observation of our IVF population will continue, it will be interesting to explore in the future whether other factors, such as severe acute respiratory syndrome coronavirus 2 and vaccination status, may affect outcomes. The question whether there might be an interaction between educational level and parity, or delayed infertility, are equally interesting to research further. The results suggest a potential direction for future research into a causal relationship between neighbourhood SES and IVF outcome.

Our results cautiously suggest that mechanisms through which neighbourhood SES influences IVF outcome may originate in the environment in which the embryo is transferred. During the in-vitro stages of the treatment, no significant differences between SES groups were found, except a minor variation in oocyte yield. In the analysis, the odds ratio on cumulative ongoing pregnancy rate for low neighbourhood SES group remained independent of the number of oocytes or embryos obtained. This suggests that the disparity may emerge from early in pregnancy, as the number of embryos obtained after follicle stimulation is linked to the oocyte reserve. There are some indications in small studies that the intestinal microbiome is associated with socioeconomic status (*Miller et al., 2016*; *Lapidot et al., 2021*), hypothesizing that an altered endometrial microbiome in women originating from low SES may influence implantation. For now, these are just speculations, and more research is needed on this subject.

In conclusion, the pr esent study suggests that residing in low SES neighbourhood is associated with a reduced probability of achieving an ongoing pregnancy within 2.5 years of IVF treatment. These disparities persist even with equal access to care, suggesting that factors beyond financial status play a significant role. The mechanism that explains our results is likely multifactorial. High overall stress (unmeasured) lifestyle factors and environmental factors are potential mechanisms behind the found associations. Further research is needed to uncover the underlying causes of this association and explore potential biological mechanisms.

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AUTHOR'S ROLES

JS, ES, and EB designed the clinical study; JS, EM and LB designed the statistical analysis; JS collected data; JS, EM and LB analysed the data and all authors interpreted the data; JS and EM drafted the manuscript; EB, ES, JL and LB substantively revised the manuscript; all authors have given approval for publication of the present version of this manuscript.

STATEMENT

During the preparation of this work the author(s) used ChatGPT to check the original grammar and word choice. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

DATA AVAILABILITY

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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