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Do quality improvements in assisted reproduction technology increase patient numbers in a managed competition setting?

Niek W. Stadhouders | Jan A.M. Kremer | Patrick P.T. Jeurissen | Marit A.C. Tanke

Radboud Institute for Health Sciences, IQ Healthcare, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence
Niek Stadhouders, Radboud Institute for Health Sciences, IQ Healthcare, Radboud University Medical Center, Nijmegen, The Netherlands.
Email: niek.stadhouders@radboudumc.nl

Summary

In a system of managed competition, selective contracting and patient choice reward providers for quality improvements through increases in patient numbers and revenue. We research whether these mechanisms function as envisioned by investigating the relationship between quality improvements and patient numbers in assisted reproduction technology in the Netherlands. Success rate improvements primarily reduce volume as fewer secondary treatments are necessary, but this can be compensated by attracting new patients. Using nationwide registry data from 1996 to 2016, we find limited evidence that high-quality clinics attract new patients, and insufficiently as to compensate for the reduction in secondary treatments. The net effect of quality increases appears to be a small decline in revenue. Therefore, we conclude that patient choice and active purchasing reward quality improvements insufficiently. Nevertheless, clinics have improved quality drastically over the last years, showing that financial incentives are perhaps less important factors for quality improvements than factors such as intrinsic motivation and professional autonomy.

KEYWORDS

assisted reproduction technology, managed competition, patient choice, quality improvements, selective contracting

1 | INTRODUCTION

Governments and health insurers aim to increase the (experienced) quality of care and the population health while containing costs, the so-called triple aim.[1,2] Quality improvements are propagated often as a means to reduce costs. Assisted reproduction technology (ART) treatment is a good case study for this: Higher success rates lower the number of attempts and therefore lower costs and—presumably—increase patient satisfaction.

ART is an alternative when natural pregnancy fails. Treatment cycles start by ovarian hormonal stimulation, after which one or more eggs are retrieved. Eggs are then fertilized in vitro (IVF), or a sperm cell is injected directly into the egg (ICSI). In about 90% of cycles, one or two fertilized eggs are placed in the uterus. Additional fertilized eggs from the same cycle can be frozen in (cryopreservation), thawed, and placed in the uterus after a first attempt failed. This reduces the burden of starting a full new treatment cycle.

In the Netherlands, three treatment cycles are reimbursed as part of the mandatory benefit package, that is, if certain preconditions (age and body mass index) are fulfilled. Tariffs are set by the Dutch Healthcare Authority (Table 1), while volumes are freely negotiable. Success rates are defined by the percentage of 10-week pregnancies over the total number of treatment cycles.[4,5] In 2016, 13 458 treatment cycles were started, of which 6486 involved IVF and 6972 involved ICSI. An additional 12 116 embryos were placed after cryopreservation. Of the 13 458 cycles, 4781 10-week pregnancies were obtained, a success rate of 36% (Table 1).

Total success rates per started treatment cycle have increased drastically, from under 20% in 1997 to 27% in 2010 to 36% in 2016. Compared with other European countries, success rates are higher only in Sweden and Finland.[6,7] One possibility to boost success rates is to place multiple embryos at the same time. This increases the number of twins and triplets, which is a risk factor for complications. Multiplets are for that reason regarded as an undesirable outcome. However, over the past years, the percentage of multiplets dropped spectacularly in the Netherlands, from 23% of 10-week pregnancies in 2003 to 3.8% in 2016. Therefore, increases in the success rate increase did not come at the cost of increased risk of complications.

Cryopreservations add to success rates per treatment cycle, as each placement of a cryopreserved embryo is considered part of a previous treatment cycle. Increases in the use of cryopreservation will therefore increase the success rates and the total number of pregnancies. It is also cost-effective: At current tariffs, an investment of

TABLE 1 Descriptive statistics on prices, quality, and volumes of ART in the Netherlands in 2016 (2010)

	Treatments 2016 (2010)	10-week Pregnancies 2016 (2010)	Success Rate[a] 2016 (2010)	DRG Tariff 2016 (2010)	Expenses per Pregnancy 2016	Total Expenses (Million Euro) 2016 (2010)
IVF cycles	6486 (8750)	1240 (1683)	19 (20) percent	€1959 (€1712)	€10 400	12.7 (16.4)
ICSI cycles	6972 (7843)	1627 (1846)	23 (23) percent	€2225 (€2172)	€10 062	15.5 (19.5)
Cryo-preservations[b]	12 116 (6729)	1914 (1055)	15 (16) percent	€444 (€305)	€2931	5.4 (2.2)
Total		4781 (4584)	36 (27) percent			33.6 (38.2)

Abbreviation: ART, assisted reproduction technology.

[a]Each treatment cycle consists of placement of an embryo through either IVF or ICSI plus one or more embryo transfers through cryopreservation. The total mean success rate is therefore higher than individual IVF ICSI success rates.

[b]All cryopreservations are part of either an IVF cycle or an ICSI cycle and add to the success rate of the treatment cycle.

Source: Vektis[3] and NVOG (2010-2016).

€10.000 is required to obtain a 10-week pregnancy for IVF and ICSI, while this is under €3.000 for cryopreservation. Therefore, extended use of cryopreservation is expected to improve ART outcomes at lower costs. However, due to much lower reimbursements, higher intensity of cryopreservation also reduces per patient reimbursements for clinics. Total reimbursements dropped from 38 million in 2010 to 34 million in 2016, which can largely be explained by increased success rates and uptake of cryopreservation.

For individual clinics, higher success rates reduce the number of treatments and thus reimbursements per patient. Thus, a financial disincentive for quality improvements exists. On the other hand, in a competitive environment, improved success rates could attract new patients and increase total treatment volume. To attract new patients, two mechanisms coexist: patient choice and selective contracting of health insurers.[8] Preconditions for patient choice appear excellent: ART is an elective treatment, outcomes in terms of success rates are highly valued by patients,[9] and the success rates of clinics are known.[4] Due to the favorable preconditions for patient choice in AR, it can be considered a best case study. Patient choice for quality has been demonstrated in a number of studies.[8,10] Other research in the Dutch context has previously found patient responsiveness to quality indicators for angioplasty and hip replacement.[11,12]

In addition, conditions for selective contracting are compelling. In 2006, Dutch health care reform introduced managed competition: insurers compete for patients under a mandatory coverage, where risk equalization prevents cherry picking. Competition on premiums incentivizes insurers to purchase actively to improve provider quality and reduce the cost of care. ART is a field in which insurers can clearly attain both of these goals: Steering patients to high-quality providers can increase quality and reduce costs. Therefore, we expect that insurers seek to steer patients through selective contracting and active purchasing strategies, especially after the 2006 reform.[8,10]

For clinics, we therefore expect quality improvements to pay off in terms of revenue due to additional patient streams.[8,13] Furthermore, we expect that this effect increased after the 2006 reform. The relation may be influenced by demographics, as regional changes in the number of eligible patients (women aged 30 to 40) can influence clinic patient numbers. Also, travel time may be of influence.[14] Patients have to visit the clinic a number of times in a short time span, which could reduce willingness to travel long distances.[15] Therefore, we expect the relation between success rate and market share of the clinic to be stronger in regions where multiple clinics are within traveling distance.[10] From these premises, we can formulate the following hypotheses:

1. Changes in success rate are positively related to changes in the number of treatments.
2. This relation is stronger after the reform in 2006.
3. This relation is stronger in more competitive regions.

The paper is structured as follows: The next section presents the research method, after which our results are presented. We end with a discussion and policy recommendations.

2 | METHODS

To analyze the relation between success rate improvements and growth in the number of treatments, we use a panel database from 1996 to 2016, routinely collected by the Dutch Institute for Obstetrics and Geriatrics (NVOG). This institute annually sends questionnaires to the heads of department of all clinics to collect data on the number of started treatments, the number of placed embryos, the number of 10-week pregnancies, and the number of twins/triplets. Data on demographics were derived from the Dutch Statistical Bureau.[16] We define a variable (R), which is 1 when the clinic is in a competitive region, defined as the dense Randstad Area, and 0 if otherwise.[13] Success rates are published with a 1-year delay, which means that patients and insurers are expected to base their choice for the clinic in year t on quality data of year $t-1$ and earlier. We test the first hypothesis by employing a fixed-effects panel regression:

$$T_{it} = \beta_0 + \beta_1\sigma_{i,t-1} + \beta_2 D_{it} + e_i + u_{it}, \tag{1}$$

where T is the number of treatments in clinic i in year t. The success rate is given by σ, while D (demographics) is the number of women between 30 and 40 in the province. As a robustness check, we test different lag structures.

The coefficient β_1 contains the combined effect of two contradicting mechanisms: Increased quality primarily reduces the number of secondary treatments, while as a secondary effect, it potentially increases the number of new patients through patient choice and/or active purchasing by insurance companies. In order to test whether quality improvements attract new patients, the secondary mechanism needs to be isolated. However, our database does not contain information on individual patients. Therefore, on a patient level, no distinction can be made between first and secondary treatments. However, we are able to calculate the effect of improved success rates on the number of secondary treatments by assuming that the dropout rate after an unsuccessful attempt is fixed. In that case, the number of new treatments N is equal to

$$N_{it} = T_{it} - x*\left(1 - \sigma_{i,t-1}\right)*T_{i,t-1},$$

where x is the dropout rate. We use a fixed dropout rate of 50%. In Germany, dropout rates between 40% and 50% are reported.[17,18] For sensitivity analysis, we range the dropout rate between 30% and 70%. To disregard general trends in the number of patients, we calculate market shares m:

$$m_{it} = \frac{N_{it}}{\sum_{i=1}^{13} N_{it}}*100 \qquad i = 1, 2, .., 13.$$

The regression specification is

$$m_{it} = \beta_0 + \beta_1\sigma_{i,t-1} + \beta_2 D_{it} + e_i + u_{it}. \tag{2}$$

To test the influence of travel distance, we interact the coefficient with a competitive region dummy (R).[13] To test the effect of managed competition, we add interaction coefficient dummy C, which is 1 after the reform. Next, we estimate the effects of success rate on market share of new patients:

$$m_{i,t} = \beta_0 + \beta_1\sigma_{i,t-1} + \beta_2 D_{i,t} + \beta_3\sigma_{i,t-1}{}^*R_{i,t} + \beta_4\sigma_{i,t-1}{}^*C_t + e_i + u_{i,t}. \tag{3}$$

In total, we estimate three specifications: (1) estimation of the composite effect of quality on the number of treatments, (2) estimation of the effect of quality on new treatments only, and (3) estimation of the effects of competitive regions and on competitive reforms.

As additional analyses, we include instantaneous effects and longer lag periods. Quality indicators are made available with a 1-year time lag. This means that quality in year t cannot influence patient choice or purchasing in year t. However, instantaneous effects may occur due to reverse causality: By increasing the number of new treatments, quality of care may decline. Equivalently, quality of care may be improved by reducing the number of treatments. This effect could be caused by more strict guidelines and regulation supported by the government.[19] However, it also could potentially indicate cherry picking: By refusing patients with low chance of success, quality ratings may be improved. Thirdly, the effect could be caused by supplier-induced demand: Treating more new patients—who have lower chances of success—reduces success rates in the same year. All three effects could result in reverse causality, which could justify adding instantaneous quality effects.

3 | RESULTS

Table 2 shows descriptive statistics for the 13 clinics in 2015. Success rates display a broad spread, ranging from 23.4% in Groningen to 40.6% at the VU Amsterdam. This appears unrelated to the number of treatments, ranging from 370 in Maastricht to 1825 in Rotterdam. Of all treatments, about two-thirds are estimated to be primary treatments.

3.1 | Main specification results

Table 3 shows the main results. No significant relation is found between the number of treatments in year *t* and the success rate in the previous year (specification 3.1). This negative sign may signal that the effect of reduced number of secondary treatments outweighs the increase in new patients. Also, no significant effect of the success rate in the previous year on the market share of new patients is found (specification 3.2). This absence of a significant positive relation persists when interacting with region and reform (specification 3.3). We conclude that no significant relation is present between quality of care and the number of (new) treatments or the market share of the clinic.

When multiple lags are tested (Table 4), significant immediate and lagged negative effects are found on the number of treatments (specification 4.1). This indicates reverse causality: Reduction of new treatments improves quality rates. Regardless of this instantaneous effect, the 1-year lagged effect of quality on market shares (specification 4.2) captures the effect of quality improvements on patient choice and purchasing. Specification 4.2 shows that a 10% improvement in the success rate is significantly associated with a reduction in market share of 0.98 percentage points in the same year, and an increase of 0.74 percentage points in the next year. The latter effect is more pronounced in competitive regions (specification 4.3). The market-based reform by itself does not have a significant influence, as no significant difference in the effect is found before and after reform. The effect slightly increases after the reform by 0.2 percentage points in competitive regions and 0.005 percentage points in noncompetitive regions; both effects are

TABLE 2 Descriptive statistics of AR clinics in the Netherlands in 2015

	5-Year Mean Success Rate (SD)	Number of Treatments	Number of New Patients (Market Share)	Demographics	Travel Time to Nearest Competitor in Minutes
Amsterdam (AMC)	28.6% (2.5%)	966	643 (7%)	182 439	10
Groningen (UMCG)	23.4% (2.4%)	671	430 (5%)	31 469	64
Maastricht (MUMC)	26.3% (2.4%)	370	233 (3%)	56 815	66
Nijmegen (Radboud UMC)	27.4% (2.7%)	1278	790 (9%)	111 513	52
Rotterdam (Erasmus UMC)	29.1% (2.6%)	1825	1221 (14%)	230 357	23
Utrecht (UMCU)	31.0% (3.1%)	1473	1007 (11%)	81 895	33
Eindhoven (Catharina ZKH)	25.0% (2.9%)	661	444 (5%)	141 529	28
Tilburg (Elisabeth ZKH)	30.0% (2.3%)	974	698 (8%)	141 529	28
Leiden (LUMC)	33.0% (2.1%)	800	554 (6%)	230 357	15
Leiderdorp (MCK)	30.1% (1.9%)	877	549 (6%)	230 357	15
Zwolle (Isala)	26.4% (2.9%)	1388	889 (10%)	65 200	55
Voorburg (Reinier de Graaf)	29.3% (2.1%)	574	356 (4%)	230 357	23
Amsterdam (VU)	40.6% (2.1%)	1611	1105 (12%)	182 439	10

Abbreviation: ART, assisted reproduction.

TABLE 3 Regression results

	3.1 Number of Treatments	3.2 Market Share of New Patients	3.3 Interaction With Region and Reform
Success rate in *t* − 1	−893.3	4.069	1.435
Interaction with region			3.967
Interaction with reform			2.887
Interaction with region and reform			5.849
Demographics	−0.00024	0.0000104	0.0000134
Time trend	17.3	−0.00623	−0.0292
Constant	−33303	17.57	63.31
N (*i*,*t*)	245 (13,20)	245 (13,20)	245 (13,20)
R^2	0.0039	0.0172	0.0032

*$P < 0.10$.

**$P < 0.05$.

***$P < 0.01$.

TABLE 4 Lag structure regression results

	4.1 Number of Treatments	4.2 Market Share of New Patients	4.3 Interaction With Region and Reform on Quality in Year *t* − 1
Success rate in *t*	−1830.356***	−9.849**	−11.866***
Success rate in *t* − 1	−481.751**	7.402**	1.650
Success rate in *t* − 2	371.7013	4.236	2.859
Interaction with region			11.290**
Interaction with reform			2.161
Interaction with region and reform			13.159**
Demographics	0.0071	0.000019	9.97e−06
Time trend	34.275**	0.0395	0.00628
Constant	−68321.3**	−74.94	−6.233
N (*i*,*t*)	243 (13,19)	243 (13,19)	243 (13,19)
R^2 (within, between)	(0.1635, 0.0449)	(0.0845, 0.0319)	(0.1275, 0.0052)

*$P < 0.10$.

**$P < 0.05$.

***$P < 0.01$.

not significant. Actual competition seems to matter more than competitive reforms. This finding is robust to alternative definitions of years, dropout ratios and competitive regions (see Appendix A). In conclusion, a positive effect of quality improvements on new patients may be present, but it is insufficiently large to provide financial incentives for clinics to improve quality.

4 | DISCUSSION

We demonstrate that quality improvements in ART have no significant effect on the number of treatments, despite what might be expected under the model of managed competition. Our results indicate that both patient choice and active purchasing fall short as means to stimulate efficiency. Patient choice may depend on nonsuccess rate dimensions of quality, such as personal contact of physicians or of the actual travel time to the clinic. We do find evidence that the impact of patient choice increases when the distance to the nearest clinic is reduced. Possibly limited patient knowledge may explain low responsiveness.[20] General physicians (GPs) acting as gatekeeper should inform patients or influence patient choice.[21] It is unknown whether GPs routinely use available quality information.

Regarding active purchasing, results indicate that at the moment, the system of regulated competition in the Netherlands does not stimulate active purchasing for assisted reproduction. As preconditions for active purchasing are better for ART than nearly any other treatment, it might be hypothesized that active purchasing by itself is falling short of policy expectations. This could be explained by low acceptance of insured patients to steering from third parties; patient choice is considered an important moral value. It could also reflect hospital market power, as resistance against selective contracting can be severe.

To improve the public's acceptance of selective contracting, insurers could increase transparency in terms of price and quality.[22] However, selective contracting is only a viable option in competitive regions. This could result in a health gap between the urban and rural regions, if predominantly urban regions are motivated to improve quality. Indeed, our results already indicate somewhat higher success rates in the more competitive regions. Furthermore, over the last couple decades, quality has improved and costs were reduced in absence of active purchasing and despite perverse financial incentives. Our results stipulate the importance of professional autonomy of medical specialists as a means of quality improvement. The role of health insurers may be limited to stimulating professional development through, eg, trans-clinic learning programs.

This study is contributing to the literature by elucidating the effects of mechanisms of patient choice and active purchasing on incentives to increase quality in a regulated competition setting. This study has several limitations. Firstly, as data are restricted to number of treatments, dropout rates and transfers to other clinics are unknown. However, our results are robust to different dropout percentages in modeling. Secondly, background characteristics of patients are unknown. Some of the differences in success rates may be explained by case mix, as clinics focusing on more complicated cases may have lower success rates. However, due to the certificate-of-needs status of ART clinics, no differentiation or specialization between clinics may be expected. Clinics may also employ patient selection and cream skimming.[23] The negative correlation in the same year between success rates and patient numbers supports this. However, the large number of patients in the VU Amsterdam, which is best performing with high patient numbers, suggests that cream skimming may not be a major concern. This is supported by relatively strict guidelines for ART in the Netherlands. However, it would require additional research to definitely rule out patient selection.

To conclude, we found that patient choice and active purchasing is functioning insufficiently to reward clinics for quality improvements. Dutch ART clinics have no financial incentive for quality improvements. Despite a lack of financial stimulus, quality has improved drastically over two decades. This indicates that technological innovations and the intrinsic motivation of health professionals are the dominant mechanisms to improve the quality of care. Currently, both active purchasing and patient choice do not perform sufficiently well to ensure efficient functioning of the “market” for AR. If policy makers seek for an effective system of regulated competition, they need to either stimulate active purchasing by insurers, active choice by patients, or both.

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ORCID

Niek W. Stadhouders https://orcid.org/0000-0002-7296-2335
Jan A.M. Kremer https://orcid.org/0000-0002-0495-0201
Patrick P.T. Jeurissen https://orcid.org/0000-0002-4198-2448

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data used for this research is available upon request or can be accessed through the following link: https://www.degynaecoloog.nl/nuttige-informatie/ivf-resultaten/

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APPENDIX A

ROBUSTNESS CHECKS

A.1 | Reform years

Table A1 shows the result of alternative definitions of the reform year. It could be that the reform was anticipated, suggesting a stronger effect when 2006 is taken as a reform year. Also, it could be that the reform took time to implement, suggesting a stronger effect when 2008 is taken as a reform year. In 2012, ex-ante compensation was reduced to improve active purchasing. We research in regression 3 whether the effect was stronger after 2012. We find that the choice of reform year does not influence the results. No significant differences between the alternative specifications were found. We can conclude that the reform did not have a significant influence on the relationship between quality improvements and new patients.

A.2 | Dropout rates

Our model assumes a 50% dropout rate. However, in literature, this figure is surrounded with a high degree of uncertainty. Therefore, we test alternative assumptions regarding the dropout rate in Table A2. We find similar results for all dropout rates, although the size of the effect declines for higher dropout rates. Therefore, we conclude that the

TABLE A1 Reform years regression results

	1 Reform After 2006	2 Reform After 2008	3 Reform After 2012
Success rate in *t*	−11.591***	−12.595***	−12.415***
Success rate in *t* − 1	1.233	2.418	1.124
Success rate in *t* − 2	2.978	3.426	2.995
Interaction with region	11.869**	10.180**	11.309**
Interaction with reform	1.049	3.455	1.957
Interaction with region and reform	12.583**	13.245**	13.102**
Demographics	8.32e−06	0.000014	0.00001
Time trend	0.0168	−0.00328	0.0114
Constant	−26.770	12.573	−16.170
N (*i*,*t*)	243 (13,19)	243 (13,19)	243 (13,19)
R^2 (within, between)	(0.1217, 0.0130)	(0.1393, 0.0004)	(0.1285, 0.0062)

*$P < 0.10$.

**$P < 0.05$.

***$P < 0.01$.

TABLE A2 Dropout rate regression results

	Dropout Rate 30%	Dropout Rate 40%	Dropout Rate 60%	Dropout Rate 70%
Success rate in t	−14.883***	−13.776***	−10.705***	−9.618**
Success rate in $t-1$	7.466	4.178	−0.457	−2.104
Success rate in $t-2$	3.545	2.968	2.430	2.230
Interaction with region	19.964***	15.380**	8.127*	5.567
Interaction with reform	8.628	4.883	−0.121	−1.904
Interaction with region and reform	22.267***	17.469***	9.834**	7.138*
Demographics	3.46e−06	8.07e-06	0.000012	0.0000135
Time trend	−0.0595	−0.0211	0.0216	0.0367
Constant	125.788	48.895	−36.646	−66.915
N (i,t)	243 (13,19)	243 (13,19)	243 (13,19)	243 (13,19)
R^2 (within, between)	(0.1913, 0.0408)	(0.1579, 0.0181)	(0.1077, 0.0012)	(0.0935, 0.0000)

*P < 0.10.

**P < 0.05.

***P < 0.01.

dropout rate used in this study does not alter our conclusions. However, we do assume that the dropout rate is the same for all clinics. Clinics differing in their dropout rate could significantly influence the results. Specifically, if high quality is combined with a high dropout rate, the effect of quality improvements on new treatments is larger, while if high quality is combined with a low dropout rate, the effect is smaller. One can assume that if quality is higher, the dropout rate will be lower, suggesting that our estimates are conservative. However, the results on the number of treatments is unaffected by the dropout rate (specification one). We can therefore definitely conclude that higher success rates have no significant effect on the total number of treatments.

A.3 | Competitive region definition

Other authors have used the Randstad area as definition of a competitive region.[13] Other definitions are also possible, which may influence the results. We test two alternatives: one narrower definition, which focuses on four clinics which are very close to each other (within 15 min of travel time), one broader definition, which is defined as the Randstad area including Tilburg and Eindhoven (all have competitors within 35 min of travel time). Furthermore, we separately test the effect of travel time to the nearest competitor in minutes as effect modifier (Table A3). We find that the competitive effect is predominant in the four clinics that are closest to each other, but the size of the effect is very similar over the different definitions of competitive regions. The third specification confirms that travel time is a significant effect modifier: Each additional minute of travel time to the nearest competitor reduces the effect of an increase in success rate on market share by 0.4 percentage points. For example, a 10% increase in quality increases market share by 1.6% when travel time to the nearest competitor is 10 minutes, while this is 0.3% if travel time is 40 minutes. This confirms the hypothesis that patients do choose on quality when the nearest alternative is close, but the effect is too small to compensate the reductions in secondary treatments due to the increase in success rates.

TABLE A3 Competitive region regression results

	1 Narrow Definition[a]	2 Broad Definition[b]	3 Travel Time in Minutes
Success rate in *t*	−13.206***	−10.767**	−11.857***
Success rate in *t* − 1	5.404	−8.344*	
Success rate in *t* − 1 (zero travel time between competitors)			20.238***
Success rate in *t* − 2	1.015	2.769	2.321
Interaction with region	12.109**	12.851***	
Interaction with reform	3.156	−4.133	
Interaction with region and reform	16.952***	13.769***	
Effect after reform			1.769
Effect of each additional minute of travel time to the nearest competitor (before reform)			−0.4168***
Effect of each additional minute of travel time to the nearest competitor (after reform)			−0.4439***
Demographics	−4.89e−06	0.0000174	2.78e−06
Time trend	0.0106	0.00149	−0.0085
Constant	−11.278	2.115	25.069
N (*i*,*t*)	243 (13,19)	243 (13,19)	243 (13,19)
R^b (within, between)	(0.2493, 0.0308)	(0.1470, 0.0031)	(0.1775, 0.0107)

[a]This includes clinics with a competitor within 15 mins: VU Amsterdam, AMC Amsterdam, LUMC Leiden, and MCK Leiderdorp.

[b]This includes clinics with a competitor within 33 mins: UMC Utrecht, Erasmus MC Rotterdam, Reinier de Graaf Voorburg, Elisabeth Tilburg, Catharina Eindhoven, VU Amsterdam, AMC Amsterdam, LUMC Leiden, and MCK Leiderdorp.

*$P < 0.10$.

**$P < 0.05$.

***$P < 0.01$.