WORKING PAPER SERIES

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December
2021
No. 341

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Working Paper

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Abstract

The direction of scientific research could depend on political interventions. To clarify how they affect science is significant to design science policy appropriately. This study investigates how political prohibition on human embryonic stem cells affects scientific research. The analysis focuses on polices of countries where affiliated organizations of first authors are located and examines whether they affect scientists' stem cell choices to study cardiac repair and regeneration. The data is constructed from published articles that are collected using PubMed search. The results demonstrate that countries' prohibitive policies partly decreased the number of articles that used embryonic stem cells. The conclusion is that prohibitive decisions bias the composition of stem cells chosen for cardiac research.

Keywords: Political interventions; Stem cells; Cardiac regeneration

1. Introduction

The direction of scientific research could depend on political interventions. Targeted public funding based on science policy provides scientists with incentives to follow political intention. Although public funding for academic research has gained a positive evaluation from previous research, the effects of politically directed research on

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subsequent science have room to be discussed. The contributions of public funding to science have been explained by market failure rationales and promotion of leading research (Arrow, 1962; Dasgupta and David, 1994; Edler and Fagerberg, 2017; Packalen and Bhattacharya, 2020; Nelson, 1959). It financially supports research that is underinvested by the private sector. Besides, scientists are likely to stick to the previous research for stable performance and to avoid choosing emerging subjects that are uncertain to achieve the same level of prior performance (Foster, Rzhetsky, and Evans, 2015). Targeted public funding is an effective incentive for scientists to try emerging research subjects. Meanwhile, how targeted fund allocation affects composition of scientific knowledge, or whether that biases scientific knowledge, remains unclear. Scientists would have incentives to choose politically targeted research subjects to gain public grants and be unlikely to choose subjects that are excluded from the target and are restricted politically. If the political target for specific technologies' research causes a strong bias in scientists' choices, accumulated knowledge would converge on the subject that is in line with the intention of policy. However, there is uncertainty as to whether targeting in policy would provide the best path for scientific advance. Thus, the effects of politically driven knowledge accumulation on the evolution of science need to be clarified for designing science policy appropriately (Fortunato et al., 2018).

To investigate the effects of targeting in policy on the choices of research subjects, this study focuses on a relationship between prohibitive policy for human embryonic stem cell (hESC) and scientists' choices of stem cells to study cardiac repair and regeneration. Stem cell research has been a significant target of science policy that promotes leading research. The foci of policies include prohibition and restriction on the use and development of hESC and promotion of research about other stem cells including induced pluripotent stem cell (iPSC). Prohibition means that research using human embryo is prohibited, and restriction means that the development period of hESC for research is limited to 7 or 14 days (Matthews and Morali, 2020). The reason of prohibition and restriction is that hESC has an ethical issue because it is generated using human blastocyst. Some countries adopt policy that prohibits the use and derivation of hESC, and others' policy restricts its development period. Research using embryonic stem cell (ESC) that is generated from non-human embryo is not the target of prohibition and restriction. Meanwhile, human induced pluripotent stem cell (hiPSC) is generated by introducing several factors into somatic cells and could solve hESC's ethical issues.

Both ESC and iPSC are pluripotent stem cells (PSC) that could be differentiated to any body cells. They have the potential for prolonging healthy life expectancy and reducing social security costs because cellular therapeutics using them would be able to

regenerate damaged and lost adult cells that are the causes of incurable injuries and diseases by existing therapeutics. Meanwhile, there are uncertainties about their clinical applications in the future. While hESC has an ethical issue, hiPSC-derived cells have a safety concern because they risk tumor formation. Therefore, it is difficult to predict which stem cells have the most potential in the future. Under these uncertain circumstances, prohibition on hESC for research would become a factor that affects scientists' stem cell choices. Thus, this study examines their causal relationship.

The analysis focuses on how prohibitive policy for hESC affected scientists' choices of stem cells to study cardiac repair and regeneration. Clarifying the effects of policy on scientific research is crucial to design science policy that promotes leading research. The hypothesis of this study is that prohibitive policy for hESC increases the likelihood that scientists choose other PSC that include iPSC and noncardiac stem cells that include mesenchymal stem cell (MSC) and bone marrow cell (BMC). The reason to focus on cardiac research is that cardiac disease is one of the main targets of stem cell research. For example, Deinsberger, Reisinger, and Weber (2020) demonstrated that 14.5% of clinical trials that used PSC were concerned with cardiovascular diseases. Therapies by PSC require a close relationship with basic research because they depend on leading knowledge (Duran, 2018). Thus, political interventions on hESC would have crucial impacts on stem cell choices for cardiac research and its clinical application. Biased scientists' choices caused by targeting policy are assumed to create a research cluster of specific stem cells, and which stem cell cluster to be formed would depend on differences in policy on hESC and other research environments. Conclusions indicate that scientists' stem cell choices depend partly on prohibitive policy for hESC and that the composition of stem cells for cardiac research is peculiar to the respective country. Then, suggestions to correct the different composition of stem cells are to activate international research collaborations for knowledge exchange (Furman, Murray, and Stern, 2012).

The remainder of this study is structured as follows. The following section reviews literature about targeting in policy to clarify the position of this study in a stream of policy research. Subsequently, the hypothesis, methodology, and data are explained, and the results are presented. The final section concludes that the targeted policy could cause a bias in stem cell choices for research and suggests the significance of international collaboration to correct the knowledge bias.

2. Literature about Targeting in Policy

In the literature review, this study categorizes previous research about targeting in policy into three groups: targeting industry for economic growth, targeting specific

technologies and systems to resolve social/global issues, and preparing environments before targeting. The first and second groups are categorization based on a development of targeting policy. Schot and Steinmueller (2018) described that innovation policy had developed as business environments changed and demonstrated the three phases of policy development. The first phase of policy was developed to complement market failure with the aim of economic growth. The second phase of policy aimed to strengthen international competitiveness in the face of economic recession caused by the oil crisis in the 1970s. The third phase of policy had objectives to solve social/global issues such as climate change and poverty. Policies in the first and second phases targeted specific industries to achieve economic growth and global competitiveness. Policies in the third phases targeted specific technologies and systems for resolution to social/global issues. Meanwhile, the third group is based on literature about the horizontal technology policies (HTPs) that emphasized the preparation of environments for adequate policy design.

Among these three groups, firstly regarding policy that targeted industry, previous research found out that targeting policies had contributed to economic growth by allocating resources to specific industries like the steel and automobile industries. Policies targeting an industry for its growth include the provision of business opportunities through public procurement, to finance publicly research projects in the private sector, subsidies such as tax credit, and protections from foreign competition through tariff and non-tariff measures (Aschhoff and Sofka, 2009; Noland, 1993; Saxonhouse, 1983). For example, public procurement of new technologies for the public service is regarded as a tool of innovation policy (Aschhoff and Sofka, 2009). Additionally, the enhancement of international competitiveness became the reason to target industry in globalization of economic activities. For example, Edquist and Zabala-Iturriagagoitia (2012) analyzed six cases about public procurement in Sweden, Norway, and the United States (the USA) and found that public support targeted for specific industry had been effective in strengthening vulnerable technical capabilities and enabling the industry to survive in international competition. Besides, targeting policy in Japan contributed to accumulating and allocating capital and labor to strengthen industry's international competitiveness (Noland, 1993; Saxonhouse, 1983).

Meanwhile, political interventions also have negative impacts on industry. Brahm (1995) found that rivalry competition was intensified by overinvestment due to incumbents' responses to politically subsidized organizations' investment in high-technology industries in the USA. Furthermore, Beason and Weinstein (1996) demonstrated that targeted policies in 1955–90's Japan decreased the factor productivities of industries. They explained that the reason was inappropriately targeting. The targeted

industries included low growth sectors like mining. Once the economy has grown to some extent, traditional policies targeting industries could be inefficient because of the difficulty involved in target selection.

The second group of literature focuses on policy that targeted specific technologies and systems to resolve social/global issues. In recent years, studies about policies that target technologies that promote innovation make a research cluster around resolution to social/global issues (Schot and Steinmueller, 2018; Weber and Rohracher, 2012). Politically targeting specific technologies could increase the number of relevant research and innovation. Hottenrott and Lopes-Bento (2014) found that policy that targeted international collaboration and research and development (R&D) at small and medium-sized enterprises had increased R&D spending and high impacts on increasing sales from products that were new to market. Examples of target for specific technologies include the latest technologies of life science to provide a cure for specific diseases. Sampat (2012) examined how to make a balance between science and health targets at the National Institutes of Health (NIH). The peer-review system for fund allocation at the NIH was difficult to concentrate funds on specific technologies. Thus, contractual funding and research centers for definite purposes like cancer treatment were effective to target research for specific diseases. As for policies that target systems to find solutions to social/global issues, Uyarra, Zabala-Iturriagagoitia, Flanagan, and Magro (2020) described that public procurement of health innovation platform contributed to setting institutions that solved social issues brought by reginal aging populations in Galicia. Regarding the political targeting of social/global issues, Sandén and Azarb (2005) suggested the significance of setting both short and long-term targets such as carbon reduction in the manufacturing industry and public support for technological innovation that enabled to generate eco-friendly products.

The third group is literature that focuses on the preparation of the environment prior to targeting. Breznitz (2007) and Avnimelech and Teubal (2008) investigated the adequate business environment for targeting policy by analyzing the causes of the successful high-technology industry in Israel. They explored the effectiveness of HTPs that aimed to promote socially desirable technological activities without targeting specific industries and technological areas (Teubal, 1997). In Teubal (1997), socially desirable technological activities mean to conduct innovation-related activities and to build advanced technological infrastructure in economically developed countries' context. Policymakers could develop targeting policy with sufficient preparation by HTPs (Avnimelech and Teubal, 2008). As examples of adequate environments, Breznitz (2007) described that the keys to the success of the information technology (IT) industry in Israel

were public support for R&D that was relevant to IT and business relationships with the financial sector in the USA. Additionally, Avnimelech and Teubal (2008) demonstrated the effectiveness of evolutionary targeting that changed policy targeting dynamically in line with the business environments. Their references to HTPs indicate the significance of external environments in success of targeting in policy.

In previous studies, the primary questions about targeting in policy have been whether public investment in industry could offset market failure in R&D investment by the private sector and whether public support would contribute to improving academic and business performance for political objects. Because their foci have been to investigate the effectiveness of targeting, the dynamic effects of targeting policy on science are difficult to accumulate knowledge (Finkelstein, 2004). Uyarra, Zabala-Iturriagagoitia, Flanagan, and Magro (2020) described that market failure rationales for policies had little care about the direction of innovation. Additionally, policies with narrowly defined targets aim to drive innovation to a definite direction for achieving political objectives. Thus, policy-driven knowledge accumulation is worth investigation to estimate what effects targeting policies would have on the progress of science. Therefore, this study would analyze the effect of prohibitive policy for hESC on subsequent studies and add practical evidence to the stream of research about targeting in policy.

3. Hypothesis

The objective of this study is to examine effects of political intervention that prohibits the use and development of hESC on the composition of stem cells for cardiac research. Political interventions on hESC for research have prohibitive, restrictive, and promotive patterns to use and develop it. Prohibitive and restrictive polices impose legal prohibitions or restrictions on the use and development of hESC because of ethical issues. Promotive policy provides public support for research using specific stem cells. For example, much public support has been directed for iPSC research in Japan because it could provide solutions to hESC's ethical issues and contribute to growing the regenerative medicine industry by providing new treatment for incurable diseases at present and new tools for drug discovery (Azuma and Yamanaka, 2016).

The reason to focus on prohibitive policy is to clarify the dynamic effects of prohibition for hESC on stem cell research. While regulating the use of hESC for research is necessary from the ethical perspective, the effects on the decrease and increase in medical and academic performance of neighboring fields by political interventions need to be investigated. Promotive policy for specific stem cells is simply expected to increase the number of studies about targeted cells. Meanwhile, prohibition on hESC could reduce

relevant research and drive scientists to study the other stem cells. The best stem cell for clinical application in cardiac repair and regeneration remains unclear (Hashimoto, Olson, and Bassel-Duby, 2018). Prohibitive policy would be the definite reason why scientists do not choose hESC for research. To investigate the impacts of prohibitive policy on the composition of stem cells leads to identify the trend of respective stem cells chosen for research. The analysis focuses on the effects of prohibitive policy on scientists' choices of stem cells including iPSC and MSC/BMC because it is suspected that prohibitions on hESC would become a hurdle to use it and induce scientists to use its alternative stem cells.

Existing research examined the effects of restrictive and prohibitive policies on hESC by federal and state government in the USA on scientists' behavior (Alberta et al., 2015; Levine, 2012; Levine, Lacy, and Hearn, 2013). Furman, Murray, and Stern (2012) found that federal restrictive funding on hESC in 2001 led to decrease the number of hESC research in the USA. The USA's share, identified by reprint authors, in citing articles declined in hESC research after 2001, though this was not the case in RNAi research. They explained this decreasing share of hESC research to be the result of restrictive federal funding that targeted hESC. Whereas their research interest was limited to hESC, this study examines the impact of prohibitive policy for hESC on all species of stem cell research. The purpose of expanding data from human to all species in this study is to examine the dynamic effect of targeted prohibitive policy. This study is not the first to expand data to other species. In previous research, Huang and Jong (2019) found that restrictive policy on hESC decreased rates of initiation and continuities of cell therapy projects by firms in the USA. Their data of corporate projects were unlimited to hESC studies because the number of hESC projects alone was too small to analyze (Huang and Jong, 2019). Prohibition on hESC is assumed to drive scientists to choose stem cells other than ESC and undermine scientists' belief in the further development of ESC. The investigation of the change in stem cell composition would add evidence for the impact of prohibitive polices on subsequent research.

The causality between prohibitive policy that targeted hESC and stem cell choices would depend on scientists' forward-looking decisions of research subjects. Prohibition on the use and development of hESC increases the difficulty in future clinical applications of ESC research. The future uncertainties and difficulties in the development of ESC research may be the reason why scientists avoid ESC research and choose other stem cells. To investigate how political interventions on hESC affect compositions of accumulated scientific knowledge, this study hypothesizes that political prohibition on hESC would drive scientists to choose stem cells other than ESC. In other words, though

ESC contains species other than human, scientists would avoid ESC and choose iPSC, MSC, and BMC because political obstacles for its use would make scientists aware of the difficulty of clinical application of their ESC research results in the future. Thus, countries' prohibitive policy would increase the number of studies about iPSC and MSC/BMC.

Additionally, this study investigates whether political interventions on hESC research cause bias in the compositions of stem cell choices. Bias in the compositions of stem cell for research could have multiple definitions. This study focuses on ESC, iPSC, and MSC/BMC research and analyzes the rate of respective stem cell in total number. Thus, biased stem cell choices in this study mean that the proportion of papers on the respective stem cell is peculiar to the respective country by responding to prohibitive policy. If prohibitive policy becomes obstacles for scientists to choose ESC and drives them for the other stem cell research, this study concludes that stem cell choices are biased by political intervention.

4. Research Method

To examine the influences of prohibitions for hESC on choices of stem cell for research, this study focuses on studies of cardiac repair and regeneration. To identify countries that have prohibitions on hESC, it follows the survey by Matthews and Morali (2020). They focused on the top 22 countries based on R&D funding in 2017 and investigated their political interventions concerning *in vitro* culture of human embryo or embryoids for basic research. Of these countries, Brazil and France have no political restrictions on its development for research. In the USA, federal funding was not allocated to research that creates or destroys a human embryo. Austria, Germany, Italy, Russia, and Turkey prohibit scientists from the derivation of hESC. Australia, Belgium, Canada, China, India, Israel, Japan, South Korea, Spain, Sweden, Taiwan, the Netherlands, and the United Kingdom have a 14-day limit in the development of hESC on research, and Switzerland has a 7-day limit. Sample data that is picked up from PubMed is narrowed down to 22 countries in Matthews and Morali (2020) by the location of the organization to which first authors belonged. The number of excluded samples and countries is 278 and 26, respectively.

In Matthews and Morali (2020), the policies for hESC in 22 countries are divided into three groups: prohibition, restriction, and permission without laws and guidelines. Countries with prohibitive policy include Austria, Germany, Italy, Russia, and Turkey, and other countries are included in a group of permissive policy, albeit some with restrictions. Thus, the sample data in this study are split into two groups: prohibiting the use and development of hESC for research and permissive for that with/without

restrictions. This study examines whether political approaches to hESC in two groups explain differences in scientists' choices of stem cells. It assumes that scientists in countries that have prohibitive policies are likely to avoid choosing ESC for research.

An observation is the choice of stem cell for cardiac repair and regeneration in an individual article. Because dependent variables are binary data, the analysis uses probit regression. The dependent variable is whether the chosen stem cell for research is ESC or not. Furthermore, this study investigates whether scientists choose iPSC and MSC/BMC to study cardiac research. Specifically, iPSC would be a strong candidate because it is an alternative tool for scientists without ethical issues. This study exploits its variation in the location of the first authors to identify the impact of political rule for hESC on their stem cell choices for research. The hypothesis is that political interventions in their locations are likely to influence the kind of stem cells for research. The analysis would infer that increased propensity to choose stem cell other than ESC is due to political prohibitions on hESC. Thus, the key independent variable is whether there were political prohibitions on hESC in countries where the organizations to which first authors belonged were located.

5. Data and Variables

The analysis focuses on PSC and noncardiac stem cells for cardiac repair and regeneration. Duran et al. (2018) categorized the sources of myocardial regeneration into using cells and others. Cells include ESC, somatic cell, iPSC, and cell sheets. Others include prefabricated matrices and extracellular matrices. Additionally, stem cells for cardiac regeneration have three main sources: noncardiac stem cells, cardiac-derived cells, and PSC (Hashimoto et al., 2018). The ideal cell for cell transplantation remains unclear (Garbern and Lee, 2013; Segers and Lee, 2008). Prohibitive policy on hESC would affect choices of noncardiac stem cells and PSC among three sources because ESC could be their alternative tool. Thus, the dataset is composed by articles about them. In the dataset, noncardiac stem cells include MSC and BMC, and PSC includes ESC and iPSC. Th data include both human and other species' stem cells.

The dataset was constructed from published articles that were collected using PubMed search. Sample articles were picked up in January 2021 under the following conditions about Medical Subject Heading term (MH), publication type, language, abstract, and publication year. Medical Subject Heading term of sample articles include "induced pluripotent stem cells," "embryonic stem cells," "human embryonic stem cells," "mouse embryonic stem cells," "mesenchymal stem cells," "mesenchymal stem cell transplantation," "bone marrow cells," or "bone marrow transplantation." Their

publication type is journal article, and it is not review, systematic review, retracted publication, meta-analysis, guideline, comment, and editorial. They are written in English, are published in 2009–2019, and have an abstract. Subsequently, 4,466 articles were identified when using the above criteria. Of these articles, 377 were excluded because MH did not involve one of the above words. It was turned out that 736 articles were duplicates; therefore, they were excluded. Then, 22 articles were excluded because year of publication was 2020. One article was excluded because its language was not English. Seven articles were excluded because they were conference papers. Additionally, the sample was narrowed down to articles whose first authors' affiliations were in 22 countries of Matthews and Morali (2020). Because first authors' affiliations were not in the 22 countries, 278 articles were excluded. Finally, the number of sample articles was 3,045. Therefore, the number of articles from 22 countries and excluded samples account for approximately 90% and 10% of the total, respectively.

To investigate the effect of prohibitive policy on the choice of the respective stem cell, dependent variables follow three patterns: *ESC*, *iPSC*, and *MSC/BMC*. They equal 1 if scientists choose respective stem cell and 0 otherwise. Because BMC includes MSC, they are combined into one variable. In the case that multiple stem cells are relevant to a study, variables of respective stem cell are equal to 1 in the study. The independent variable is *Prohibitive policy*. It equals 1 if a location of the first author's affiliation is in Austria, Germany, Italy, Russia, and Turkey and 0 otherwise. Control variables include *Year 2010–2019* that equal 1 if articles are published in respective year and 0 otherwise and country dummy that equals 1 if the research institute to which first author belonged is in respective country and 0 otherwise. Country dummies are set about the top 10 countries in number of articles. Thus, they include *Canada*, *China*, *France*, *Germany*, *Italy*, *Japan*, *South Korea*, *the Netherlands*, *the United Kingdom*, and *the USA*. Countries where scientists conducted research are identified by the location of the first author's affiliation in the article. When multiple affiliations about the first author are identified, the affiliation listed first is used to identify a country where research was conducted for published articles. In the case that scientists changed affiliations, the affiliations where research was conducted are usually listed first.

6. Countries' Trends in Stem Cell Choices

The sample data demonstrate that stem cell choices are unique to various countries. Table 1 shows the number of respective stem cell research by the top 10 countries in descending order of total number of articles. Table 2 shows the ranking of each country by respective stem cell. the USA, China, Japan, and Germany occupy the

top four countries in all three stem cells' studies, albeit with different trends by country. China and Japan have strength in MSC/BMC and iPSC research, respectively. The USA has published far a greater number of papers on ESC and iPSC research than other countries.

Figure 1 demonstrates the entire number of respective stem cell studies by year. The number of MSC/BMC studies remains at a near constant level, and regarding ESC, the number of studies has been gradually decreasing since 2015. Meanwhile, the number of iPSC research has increased almost constantly. This study hypothesizes that the decreasing the number of ESC research would be partly explained by prohibitive policy.

Figure 2 demonstrates the top four countries of respective stem cell research. Studies in China use MSC the most frequently, and in the USA and Japan, the number of studies that use iPSC is the highest, albeit with a different scale. Levine (2011) found that scientists in the USA faced challenges from the uncertainty of federal policy concerning hESC because the criteria for allocating federal funds to hESC research had been modified with the change of administration. Almost half of scientists in the survey answered that political uncertainty had a substantial impact on their projects. They explained that the negative impacts were caused by the delay to begin hESC research projects and the impediment to ongoing projects. Thus, although Chen and Li (2021) referred that the USA has relaxed conditions on hESC, scientists had faced the difficulty in conducting hESC research, which might affect the likelihood of choosing ESC for research.

Figure 3 shows a rate of respective stem cell in total in descending order of the rate of ESC research. The highest rate of ESC is the Netherlands, and the lowest is Russia. In the three lowest countries that are Turkey, Brazil, and Russia, the rate of research that uses MSC is over 80%. McMahon and Thorsteinsdottir (2013) explained the reason of small number of iPSC and ESC research in Brazil by the late start due to public debate about the legality of hESC research. They suggested that regenerative medicine in developing countries was strongly demanded to achieve clinical applications of stem cells. Additionally, Salter, Zhou, and Datta (2015) referred to the increasing pressures of market-based stem cell innovation from health consumers to a science-based approach. Thus, pressures from the market may facilitate MSC/BMC research in developing countries.

<Table 1. The number of stem cell research by total number's top 10 countries>

<Table 2. Top 10 countries of respective stem cell research>

<Figure 1. The number of respective stem cell research by year>

<Figure 2. Top four countries in all three stem cells' research>

<Figure 3. The rate of respective stem cell in total>

7. Results

Table 3 provides descriptive statistics and correlations for all variables. Table 4 shows the results of probit regression. This study assumes that uniqueness of various countries in scientists' stem cell choices is explained by differences in science policy. The analysis examines whether prohibitive policy on hESC affects the number of cardiac research that uses ESC, iPSC, and MSC/BMC. The results show that it reduces the number of ESC research and increases the number of iPSC and MSC/BMC research, though the extent of the influences on the respective stem cell varies by country.

Models 1–7 show the results of probit regression to investigate the effect of prohibitive policy on scientists' choices of stem cells for cardiac research. Dependent variables of Models 1–2, 3–5, and 6–7 are *ESC*, *iPSC*, and *MSC/BMC*, respectively. Models 1, 3, and 6 include full independent variables. Models 1 and 2 examine the hypothesis that prohibitive policy decreases the number of ESC research. Negative coefficients of *Prohibitive policy* in both models are statistically significant at the 5% level. Model 2 has the top four countries' dummies that have a high number of three stem cells' studies. Negative coefficients of *China* and *Japan* are statistically significant at the 5% and 1% levels, respectively, and positive coefficient of *Germany* is statistically significant at the 1% level.

Models 3–5 examine whether prohibitive policy affects the number of iPSC research. Negative coefficient of *Prohibitive policy* in Model 3 is statistically insignificant, and its positive coefficients in Models 4 and 5 are statistically significant at the 10% and 5% levels, respectively. Thus, scientists in countries with prohibitive policy are likely to choose iPSC for research. Model 5 has two countries' dummies, namely, *the USA* and *Japan*. They have a higher percentage of iPSC research than ESC and MSC/BMC in the top four countries in total number of articles. Whereas scientists in the USA have been leading the latest research areas, the high rate of iPSC research in Japan is a result of the public support that has targeted iPSC research since its discovery by Japanese scientists.

Positive coefficients of both countries' dummy variables are statistically significant at the 1% level. Because the coefficient of *Japan* is larger than that of *the USA*, scientists in Japan are more likely to choose iPSC research.

Models 6 and 7 examine the effect of prohibitive policy on scientists' choices of MSC/BMC for research. Positive coefficients of *Prohibitive policy* in both models are statistically significant at the 1% and 5% levels, respectively. Thus, they support that the number of MSC/BMC research increases in countries with prohibitive policy. Model 7 has the top four countries' dummies, namely, *China*, *Germany*, *Japan*, and *the USA*. The percentage of MSC/BMC research is high in China and low in the other three countries. The negative coefficient of *China* and positive coefficients of the other three countries' dummies are statistically significant at the 1% level. Compared to those in the other three countries, scientists in China are more likely to choose MSC/BMC for cardiac research.

Results in Models 1–7 support that prohibitive policy on hESC decreases the number of ESC research and directs scientist to choose iPSC and MSC/BMC for research. However, the impact on MSC/BMC and iPSC research depends on the country. Model 2 shows that scientists in Germany are likely to choose to study ESC, although the government adopts prohibitive policy on hESC. Meanwhile, although China is a country that adopts policies that permit the use and development of hESC with restrictions, the proportion of ESC research in total is lower than that in Germany. Countries' dummies in Model 7 indicate that scientists in China differ in their stem cell choices from those in other top countries. They are likely to choose more MSC/BMC than are those in other countries. Therefore, the extent of the effects of prohibitive policy on scientists' choices depends on countries' different research environments.

<Table 3. Descriptive statistics and correlations>

<Table 4. Results of probit regression>

8. Discussion

Results show that prohibitive policies on hESC affect scientists' choices negatively of ESC and positively of iPSC and MSC/BMC for cardiac research. Thus, the increasing trend of iPSC research and not the decreasing trend of MSC/BMC research in Figure 1 are partly explained by prohibitive policy on hESC. This study provides evidence

that prohibitive policy on hESC leads to decreasing number of ESC research. Although the impacts on MSC/BMC and iPSC research are different by country, scientists facing prohibitive policy are likely to choose stem cells other than ESC. Meanwhile, the causality about how prohibitive policy on hESC affects stem cell choices requires discussion because dependent variables contain stem cells of all species. If scientists make forward-looking decisions of research subjects, they choose iPSC and MSC/BMC, not ESC, because of its difficulty in future development. The applicability of research results about non-human stem cells to human may attract scientists' attention to non-ESC cells.

Additionally, the different responses to prohibitive policy on hESC would be caused by research environments in respective countries. Even under prohibitive policy on hESC, scientists in Germany are likely to choose ESC for research. Germany has a law that prohibits the derivation of hESC and allows to use hESC that were created before March 1, 2007, in foreign countries for research (Duran et al., 2018). Nevertheless, the difference between ESC and iPSC research in Germany is not as large as that in Japan. Löser et al. (2012) found that the number of hESC research in Germany increased regarding papers published in 2007–2011. The reason could be a result of their location that has neighboring countries with restrictive but permissive policies on hESC. Scientists in Germany would be able to easily gain the latest information on hESC, and they have an option to move to neighboring countries if they hope to study hESC under permissive policy. Thus, they could be optimistic about the development of ESC research in the future.

Meanwhile, even in countries where hESC research was permitted, the patterns of stem cell choices vary. For example, compositions of stem cells for research in Brazil and France that have no restrictions on hESC research might indicate that scientists have no clear answer for stem cell choices and that exogeneous factors, other than prohibitive/restrictive policies on hESC, affect their choices. Figure 3 shows that the rate of ESC research in France is less than 40%. This is approximately the same proportion as that in Germany that has prohibitive policy. In Brazil, over 80% of research is regarding MSC/BMC. Whereas prohibitive policy reduces the number of ESC research, other factors would induce scientists to choose specific stem cells. Future research could explore what factors other than prohibitive policy affect scientists' decisions. Additionally, China and Japan show remarkable differences among the top ten countries. They have a 14-day developmental limit on hESC (Matthews and Morali, 2020). Under the same conditions, scientists in Japan are likely to choose iPSC, and scientists in China are likely to be involved in MSC/BMC research. As Figure 3 highlights, their rate of choosing MSC/BMC is more than 50%. While a high proportion of iPSC research in Japan would be explained by generous public support for iPSC research, demand-driven pressures for

scientists in developing countries might explain China's high proportion of MSC/BMC research (McMahon and Thorsteinsdottir, 2013).

9. Conclusions and Limitations

This study examines how prohibitive policy on hESC affects the choices of stem cells for cardiac research and concludes that it generates bias in their compositions. Previous research has estimated the effectiveness of science policy by patent count and article citations (Furman, Murray, and Stern, 2012; Li, Azoulay, and Sampat, 2017; Sampat and Williams, 2019 etc.). The core contribution of this study is to add evidence that prohibitive policy could change scientists' behaviors and generate bias in accumulated scientific knowledge. Another contribution is to find variations of stem cell compositions across countries. Because MSC/BMC and iPSC become alternative tools to ESC, scientists have options to use them. How scientists respond to the policy on hESC depends on the availability of stem cells and the amount of funding available for research. They would affect the compositions of stem cell choices for research.

The first limitation of this study is that the effect of other factors on scientists' stem cell choices remains unclear. The reasons why scientists choose stem cell for research would include pure scientific interests in the mechanisms, the potential for clinical application, its availability, and the political restrictions and support for it. Although these direct factors other than prohibitive policy would affect scientists' choices of stem cells for research, some of them are not considered in probit regression. Additionally, indirect factors that include the degree of public and private investment in other stem cells, specialties of local research institutes, market demand, and public opinion would affect their choices. For example, because public opinion in Japan has supported investment in iPSC research after the Japanese scientist won the Nobel Prize, the government has designed science policies that target iPSC to take the lead in the regenerative medicine industry. Figure 3 shows that the targeting policy has significantly increased the proportion of iPSC research in Japan. Future research is necessary to identify these other influential factors qualitatively with field study and then to quantitatively clear the degree of effects on scientists' behaviors.

Another limitation is insufficient support for the causality that prohibition on hESC leads to decreasing the number of ESC research that includes other species. Whereas the focus of prohibitive policy is limited to human stem cells, dependent variables about stem cells contain all species. This study interprets that causality between prohibitive policy on hESC and decreasing the number of ESC research is explained by scientists that would predict the difficulty of subsequent clinical application with hESC.

Additionally, field study to ask authors about the reason to choose specific stem cell for research is necessary to make sure the causality.

Moreover, how locally biased choices of stem cells affect the subsequent research requires further investigation. The regional specialty of stem cell research would influence what professional scientists come to study there in the future. This means that the locally biased choice of stem cell may decide what stem cell research would be major in the region. If locally major stem cells could take an important role in future clinical application of cardiac repair and regeneration, politically directed choices would prove effective. However, predicting appropriate political direction of scientific research is difficult due to high uncertainty in the future performance of the respective stem cell. In this respect, the effectiveness of the targeting policy would require a long time to assess. Azoulay, Zivin, and Manso (2011) find that grants tolerating early failure and rewarding long-term success contribute to breakthrough performance more than do short-cycle review grants. Their findings support the idea that the grant system absorbing uncertainty in the long-term research process is effective for high performance. Therefore, science policy might need to be designed to absorb unexpected research development by non-targeting.

To correct locally biased knowledge compositions would be another solution of this issue. Regarding this aspect, the combination of regionally clustered innovation processes and collaboration with organizations outside the region are effective to complement with each other (Carayannis, Meissner, and Edelkina, 2017). Furman, Murray, and Stern (2012) found that the decreasing number of hESC research in the USA, caused by the 2001 policy decisions of the Bush administration, was mitigated by international research collaborations. Thus, international collaborations would be also the key to solving biases caused by politically targeted policy. Finally, because the focus of this study is limited to research for cardiac repair and regeneration, it is necessary to investigate wider applicability of specific conditions in this field to other fields. Future research should examine effects of targeting policy on scientists' behaviors in expanded data, including that outside of heart regeneration.

Despite these limitations, this study contributes to adding evidence about the effect of political interventions on stem cell choices by scientists for cardiac research and to showing that patterns of bias vary by countries. These contributions would be extended to future works that examine whether locally different compositions of stem cell knowledge lead to their differences of performance. In other words, because future research could identify the results of targeting policies, they should verify whether politically induced knowledge bias would be effective to the subsequent research.

Acknowledgments

This article was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (Kiban-C-21K00247).

Declaration of interest

None.

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Table 1. The number of stem cell research by total number's top 10 countries

	Country	ESC	iPSC	MSC/BMC	Total
1	The USA	356	432	320	1108
2	China	159	94	365	618
3	Germany	106	112	77	295
4	Japan	59	138	52	249
5	The United Kingdom	47	34	32	113
6	Italy	28	28	44	100
7	Canada	37	17	40	94
8	South Korea	29	11	49	89
9	The Netherlands	43	19	26	88
10	France	22	15	24	61

Table 2. Top 10 countries of respective stem cell research

Country	ESC	Country	iPSC	Country	MSC/BMC
The USA	356	The USA	432	China	365
China	159	Japan	138	The USA	320
Germany	106	Germany	112	Germany	77
Japan	59	China	94	Japan	52
The United Kingdom	47	The United Kingdom	34	South Korea	49
The Netherlands	43	Italy	28	Italy	44
Canada	37	The Netherlands	19	Canada	40
South Korea	29	Canada	17	The United Kingdom	32
Italy	28	France	15	The Netherlands	26
France	22	South Korea	11	France	24

Figure 1. The total number of respective stem cell research by year

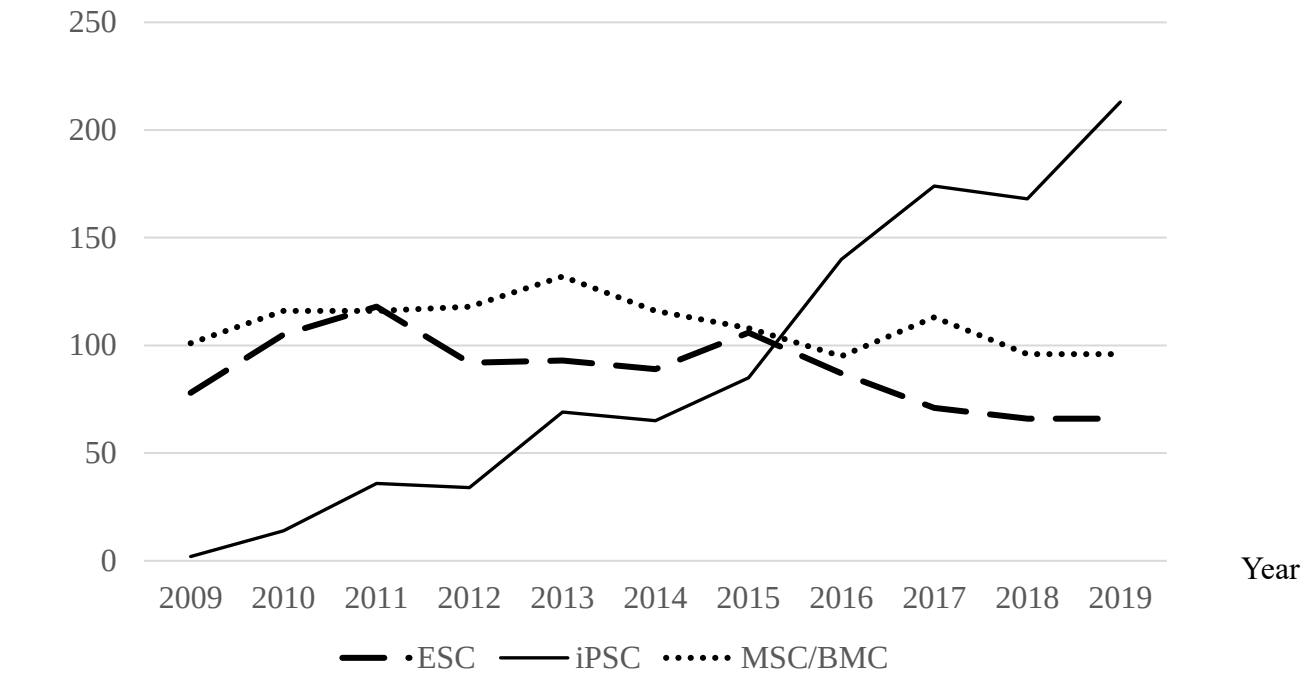

Figure 2. Top four countries in all three stem cell research

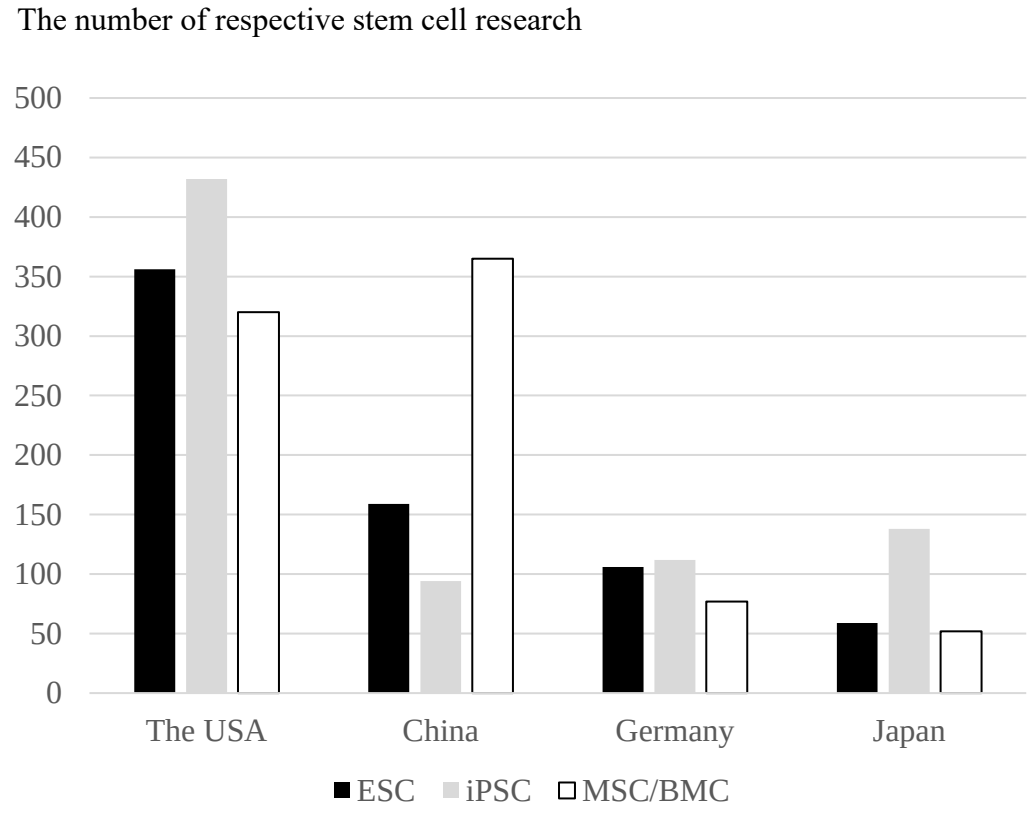

Figure 3. The rate of respective stem cell in total

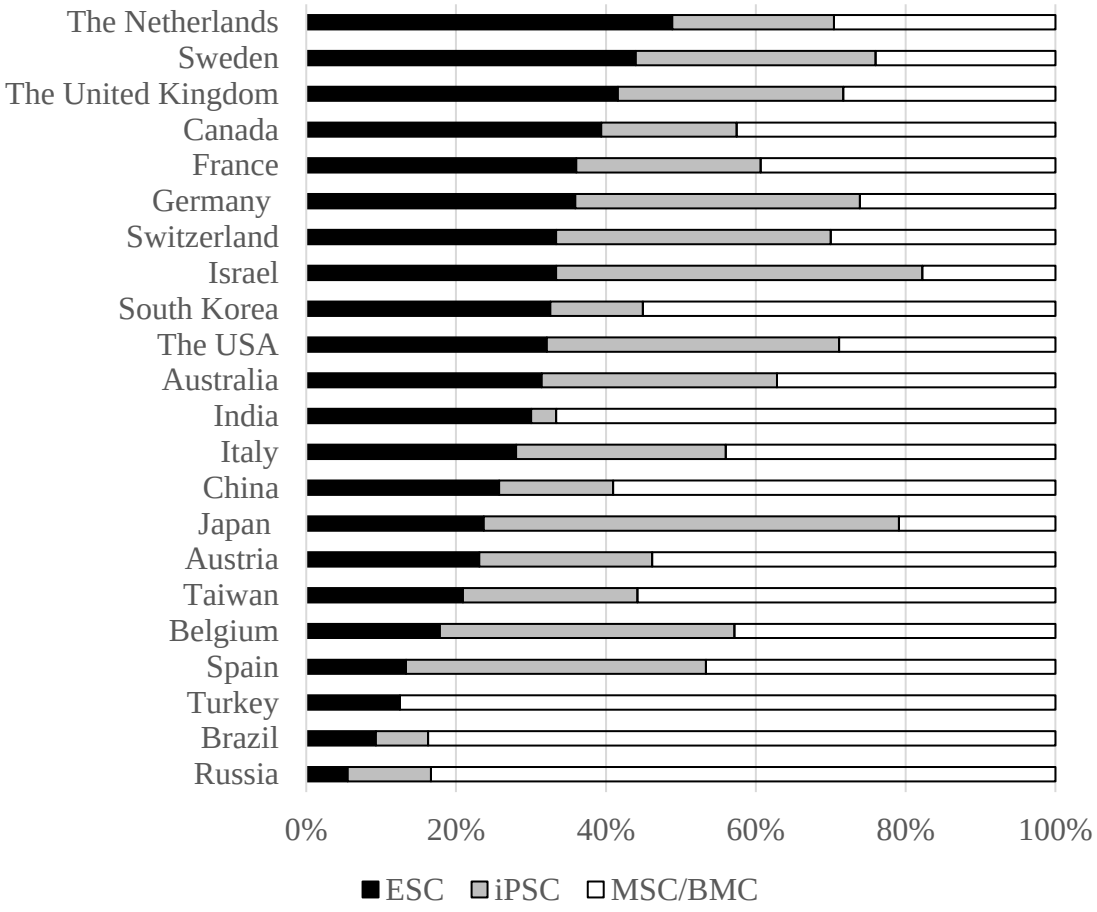

Table 3. Descriptive statistics and correlation

	Variables	Mean	S.D.	1	2	3	4	5	6	7	8	9	10
1	ESC	0.32	0.47	-									
2	iPSC	0.33	0.47	-0.34	-								
3	MSC/BMC	0.40	0.49	-0.52	-0.54	-							
4	Prohibitive country	0.14	0.32	0.02	0.02	-0.03	-						
5	Canada	0.30	0.17	0.03	-0.06	0.01	-0.07	-					
6	China	0.20	0.40	-0.06	-0.18	0.22	-0.20	-0.09	-				
7	France	0.02	0.14	0.01	-0.02	0.00	-0.06	-0.03	-0.07	-			
8	Germany	0.10	0.29	0.04	0.05	-0.08	0.80	-0.06	-0.16	-0.04	-		
9	Italy	0.03	0.17	-0.01	-0.01	0.02	0.45	-0.03	-0.09	-0.03	-0.06	-	
10	Japan	0.08	0.27	-0.04	0.16	-0.10	-0.11	-0.05	-0.14	-0.04	-0.09	-0.05	-
11	South Korea	0.03	0.16	0.01	-0.07	0.06	-0.07	-0.03	-0.08	-0.02	-0.05	-0.03	-0.05
12	The Netherlands	0.03	0.16	0.07	-0.04	-0.03	-0.07	-0.03	-0.08	-0.02	-0.05	-0.03	-0.04
13	The United Kingdom	0.04	0.19	0.05	-0.01	-0.04	-0.08	-0.03	-0.10	-0.03	-0.06	-0.03	-0.06
14	The USA	0.36	0.48	0.03	0.13	-0.14	-0.29	-0.13	-0.36	-0.10	-0.23	-0.13	-0.21
16	2010	0.07	0.26	0.09	-0.16	0.07	0.02	-0.01	-0.03	0.01	0.01	-0.02	0.03
17	2011	0.08	0.28	0.09	-0.12	0.03	0.03	0.00	-0.03	0.03	0.02	0.01	-0.01
18	2012	0.08	0.27	0.05	-0.11	0.06	0.00	0.01	-0.02	0.03	-0.00	0.01	0.01
19	2013	0.09	0.29	0.01	-0.05	0.05	-0.00	0.02	0.04	-0.02	-0.02	0.04	-0.04
20	2014	0.08	0.28	0.02	-0.05	0.03	-0.01	0.00	-0.02	-0.02	0.00	-0.01	0.00
21	2015	0.10	0.29	0.03	-0.03	-0.02	-0.04	-0.02	0.02	-0.01	-0.03	-0.02	-0.03
22	2016	0.10	0.30	-0.03	0.09	-0.06	-0.01	-0.02	0.00	0.01	0.00	-0.02	-0.01
23	2017	0.11	0.32	-0.08	0.14	-0.05	-0.00	0.02	0.00	-0.01	0.02	-0.02	0.03
24	2018	0.10	0.31	-0.08	0.15	-0.07	0.01	-0.02	0.01	-0.01	-0.00	0.04	0.03
25	2019	0.12	0.32	-0.11	0.20	-0.10	-0.11	-0.01	0.03	-0.02	-0.00	-0.00	-0.00

	Variables	11	12	13	14	15	16	17	18	19	20	21	22	23
12	The Netherlands	-0.03	-											
13	The United Kingdom	-0.03	-0.03	-										
14	The USA	-0.12	-0.12	-0.14	-									
15	2010	0.01	0.01	-0.01	-0.00	-								
16	2011	0.01	-0.01	-0.00	0.00	-0.01	-							
17	2012	0.03	0.02	-0.02	-0.01	-0.08	-0.09	-						
18	2013	-0.01	0.02	-0.02	-0.01	-0.09	-0.10	-0.09	-					
19	2014	-0.00	0.01	0.04	0.00	-0.08	-0.09	-0.09	-0.10	-				
20	2015	-0.03	-0.01	0.00	0.04	-0.09	-0.10	-0.09	-0.10	-0.10	-			
21	2016	0.04	-0.01	0.01	0.01	-0.09	-0.10	-0.10	-0.11	-0.10	-0.11	-		
22	2017	0.00	-0.00	-0.02	-0.02	-0.10	-0.11	-0.10	-0.11	-0.11	-0.12	-0.12	-	
23	2018	-0.03	-0.03	0.02	0.00	-0.10	-0.10	-0.10	-0.10	-0.10	-0.11	-0.12	-0.12	-
24	2019	-0.00	-0.02	0.01	-0.01	-0.10	-0.11	-0.11	-0.12	-0.11	-0.12	-0.12	-0.13	-0.13

Table 4. Results of probit regression

Independent variables	Dependent variables						
	ESC		iPSC			MSC/BMC	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Prohibitive policy	-0.64**	-0.33**	-0.46	0.14*	0.54***	0.61***	0.28**
Canada	0.38**		-0.36*			-0.19	
China	0.08	-0.18**	-0.62***			0.38***	0.52***
France	0.27		-0.08			-0.24	
Germany	1.00***	0.43***	0.81**			-1.17***	-0.70***
Italy	0.76***		0.40			-0.64**	
Japan	-0.01	-0.27***	0.85***		1.18***	-0.74***	-0.60***
South Korea	0.25		-0.67***			0.26*	
The Netherlands	0.64***		-0.15			-0.54***	
The United Kingdom	0.53***		-0.02			-0.46***	
The USA	0.25***	-0.01	0.34***		0.67***	-0.47***	-0.33***
Year 2010	0.12	0.09	0.71**	0.76*	0.72**	-0.12	-0.10
Year 2011	0.05	0.04	1.27***	1.21***	1.27***	-0.32**	-0.31**
Year 2012	-0.13	-0.12	1.29***	1.23***	1.28***	-0.18	-0.18
Year 2013	-0.28**	-0.27**	1.76***	1.61***	1.73***	-0.33***	-0.33***
Year 2014	-0.26**	-0.26**	1.69***	1.63***	1.69***	-0.32**	-0.31**
Year 2015	-0.20*	-0.21*	1.84***	1.74***	1.83***	-0.58***	-0.58***
Year 2016	-0.45***	-0.45***	2.29***	2.16***	2.27***	-0.77***	-0.75***
Year 2017	-0.67***	-0.67***	2.44***	2.31***	2.42***	-0.67***	-0.66***
Year 2018	-0.67***	-0.66***	2.48***	2.36***	2.45**	-0.76***	-0.77***
Year 2019	-0.75***	-0.77***	2.69***	2.51***	2.65	-0.93***	-0.92***
Constant	-0.34***	-0.08***	-2.49**	-2.31***	-2.80**	0.44***	-0.30***
LR chi-square	201.30***	169.26***	814.06***	540.70***	754.76	389.47***	356.30***
N	3,045	3,045	3,045	3,045	3,045	3,045	3,045

*p<0.1, **p<0.05, ***p<0.1