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Regional Innovation Systems of Medical Technology: A knowledge production function of cardiovascular research and funding in Europe

Rucha Vadia[1] and Katharina E. Blankart[2]

[1] University of Hamburg, Hamburg, Germany
[2] University of Duisburg-Essen, Essen, Germany

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Abstract. We investigated the role of public funding in cardiovascular device innovation across 31 countries in Europe. We rely on the knowledge production function (KPF) framework that establishes the knowledge output of a region as a function of innovatory effort and other characteristics of that region. In a cross-sectional analysis, we investigated regional variation in knowledge production by the number of publications in cardiovascular device research obtained from the bibliometric data of the world's largest biomedical library, the US National Library of Medicine, 2014–2017. We mapped these publications to product categories of medical devices approved for cardiovascular diseases by the US Food and Drug Administration. Considering spatial correlation across regions of Europe in our estimates of the KPF, we investigated the impact of two types of public funding mechanisms: the volume of European Union (EU) Framework Programme (FP) 7 funding received by the innovating regions and that of its successor the EU Horizon 2020 funding. We obtained 123,487 cardiovascular device-related publications distributed across 1,051 (75% of total) regions (NUTS-3 level). Receiving public funding strongly contributes to a region's knowledge output. The estimated elasticities of innovatory effort by FP7 range between 0.36 and 0.40 while the estimated elasticities of Horizon 2020 range between 0.13 and 0.17. Estimated elasticities remain robust after controlling for country level fixed effects. When accounting for additional inputs to the KPF by private funding and health system related factors, the elasticity estimates for FP 7 and Horizon 2020 reduced, but remained significant. We documented spillover from neighboring regions, albeit at small scale. Our results conclude that innovatory efforts in the form of public research investments are effective for promoting innovation in the medical device industry at the regional level.

JEL classification: R11, R12, O32, O52

Key words: Innovation, Regional Innovation System, Medical Technology, Cardiovascular Devices, Innovatory Spillover, Spatial Spillover

1 Introduction

In a learning economy, innovation is recognized as new knowledge resulting from user-producer interaction. In the medical device industry, knowledge generation has led to a better clinical understanding of diseases, resulting in improved medical procedures in addition to technological advancements. For example, the evolution of the left ventricular assist device began with advances in understanding heart failure, leading to improvements in the medical procedures, further improving the design of the device (Morlacchi, Nelson 2011). As in other industries, such user-producer interaction in the medical device industry may tend to cluster innovation systems that, in turn, accelerates knowledge production (Cooke et al. 1997, Asheim, Isaksen 1997, Asheim, Coenen 2005).

In this study, we analyzed regional innovation systems (RIS) of cardiovascular medical devices by accounting for the spatial distribution of knowledge and quantifying the role of public funding as an innovatory effort in a knowledge production function (KPF). The medical device industry typically ranks high in terms of its patent share in Europe – 7.7% of all patents to the European Patent Office are filed for medical devices (MedTech 2020a). The European market is the second largest in the global medical device industry (27% of revenues), with a trade surplus of about 11.7 billion Euro in 2018. However, industry activities are spread unevenly across different clusters in terms of market, employment, and trade shares. Of the roughly 32,000 companies active in the industry, 95% are small and medium-sized enterprises (SMEs) employing more than 730,000 employees across Europe. A geographical variation exists in terms of implant/usage rates of devices at both regional and country levels in Europe (Tarricone et al. 2017).

New medical devices develop from the interplay of scientific advancements, learning in medical practice, and technological development where physicians are often key contributors to device development as entrepreneurs (Morlacchi, Nelson 2011, Smith, Sfekas 2013). When interactive involvement of physicians is considered in advancing medical device innovation, the question remains how and which investments in research and development (R&D) contribute. The SMEs and physicians in Europe have depended on public and private investments, of which public funding contributes a substantial proportion (MedTech 2020b). Targeted scientific research funding and coordination by research institutes have been identified as the strongest opportunities (Maresova et al. 2015). While the distribution of public research funding on cardiovascular research is heterogeneous (Pries et al. 2018), the effectiveness of public funding from national and supranational levels such as the European Union's Framework 7 and Horizon 2020 programs on knowledge output is unclear. Previous evidence, irrespective of the industry, demonstrates the effectiveness of innovatory efforts by measuring R&D investments, human capital, and intermediary scientific institutes on the knowledge output of patents (Moreno et al. 2005, Marrocu et al. 2013, Fritsch, Franke 2004). Understanding what leads to new knowledge and subsequent innovation in the medical device industry is important because the patients with access to highly innovative clinicians and firms in their region will likely benefit from these innovatory efforts. For example, significant regional level differences in use, along with hospital mortality, were documented in the case of transcatheter aortic valve implantation by region in the United States (Gupta et al. 2017).

This study aimed to investigate the role of public funding in cardiovascular device innovation. We relied on the KPF framework that establishes regional knowledge output as a function of innovatory effort that we examined by public funding. We investigated regional variation in knowledge production by the number of publications in cadiovascular device research from bibliometric data obtained from the world's largest biomedical library, the US National Library of Medicine (NLM). We evaluated the effectiveness of receiving public funding mainly through the European Union (EU)'s funding programs on regional level knowledge production in Europe (31 countries consisting of EU-27, the UK, Switzerland, Iceland, and Norway). We further accounted for variation in private funding by capturing sponsorship received by randomized controlled trials in our publication data. In addition, we performed subgroup analyses in four countries to capture additional healthcare system level variation. We expected to find that receiving public research funding positively influences the regional knowledge output for innovation in cardiovascular devices.

2 Background

2.1 Innovation pathways in cardiovascular device research and development and health outcomes

Our study setting emphasizes cardiovascular devices because, within the medical device industry, many significant advancements have been made to improve the treatment and diagnosis of cardiovascular diseases. These include various diseases linked to heart and blood vessels, such as heart failure, stroke, arrhythmia, heart disease, and heart valve problems. Besides cancer research, advancements in cardiovascular research contributed to an increase in life expectancy of around 3.73 years in the US from 1950 to 2000 (Murphy, Topel 2006). Many cardiovascular devices are products of this research contributing to health gains; several important cardiovascular device innovations – such as electrocardiogram, cardiac catheterization, computed tomography, and magnetic resonance – were products of Noble Prize-winning research (Mesquita et al. 2015).

Our focus is on the innovation stage that lies beyond the invention of a medical device, since they undergo incremental innovation in multiple tests and validation stages before market launch and commercialization, but also post-marketing approval phases (Dziallas, Blind 2019, Tarricone et al. 2017). In this way, the innovation activity of a device is observed during the "design-build-test-redesign" cycle instead of the preliminary prototype stage. It often takes place in collaboration with physicians who experience unmet needs in their clinical practice. Physicians also take part in clinical studies where the safety and efficacy of a new medical device need to be demonstrated before adopting it into clinical practice (Kaplan et al. 2004, EMA 2019). For example, the coronary artery stents, invented by physicians and researchers, became widespread only after various clinical trials demonstrated them to be safe and effective (Xu et al. 2012, Mckavanagh et al. 2018). Moreover, user-producer interaction in the post-market approval phase is crucial (Ciani et al. 2016). In this phase, technology scope is often refined with physicians' feedback long after the initial device-design was invented. For example, the device scope of cardiac resynchronization therapy widened because clinical studies revealed its applications in new and diverse patient groups (Boriani et al. 2018). Such user-oriented and process-oriented innovations are often recorded as results of clinical studies and scientific publications. In terms of financing, such stages of testing, validation, and redesign involve academic centers that rely on various funding sources. Public funding of individual inventors and clinicians is acknowledged to foster innovation in the medical device domain (Xu et al. 2012).

Analyzing innovative activity in cardiovascular research not only has implications for knowledge production and subsequent innovation but also for cardiovascular disease-related health outcomes. More than 1.8 million deaths were attributed to cardiovascular diseases in 2016 in Europe alone (Eurostat 2016, WHO 2017). Cardiovascular morbidity and mortality are highly variable across regions, even within the same country. Patient's access to new devices remains higher in areas where adopting new devices is more likely. The role of the supply side and related physician behavior is emphasized in explaining regional variation in health outcomes in the health-economic literature (Bech et al. 2009, Cutler et al. 2019). Therefore, patients in regions with higher innovative activity have higher health benefits from the early use of innovation. As the financial burden of cardiovascular diseases is high, €196 billion in 2013 in Europe (Komajda et al. 2013), the potential of efficiency gains from knowledge production translating to the bedside is high. Although we will focus on knowledge production occurring at the incremental innovation phases (testing, validating, and post-marketing feedback), our results may have wider implications on the regional variation in the productivity of health care systems.

2.2 Regional Innovation Systems for Research and Development

Innovation systems develop via interventions received at regional levels and are typically analyzed by regional-level R&D activities (Buesa et al. 2010, Moreno et al. 2005, Cooke et al. 1997). Hence, we assume that cardiovascular device innovations emerge from regional R&D activities involving vertically interconnected actors, such as medical device manufacturers, physicians, and academia. By considering the availability of R&D investments, particularly of public funding mechanisms at the regional level, we can analyze if such opportunities promote the innovative capacity of a region.

Analyzing this capacity requires accounting for the spillover effects by innovative activities in neighboring regions as previous evidence suggests it influences the knowledge output of a region (Moreno et al. 2005, Gumbau-Albert, Maudos 2009, Marrocu et al. 2013, Bottazzi, Peri 2003). Out of four types of proximities explored in the literature that consider possible spillovers, we focus on geographical proximity (Usai et al. 2015). Previous evidence suggests that technological proximity can be even more impactful than geographical proximity when considering innovatory effort across many industrial sectors (Marrocu et al. 2013). However, we focus on geographical proximity, by analyzing regional variation in knowledge production, within the same technological field, i.e., cardiovascular devices. Social and organizational proximities are known to be less impactful when performing cross-regional comparisons (Marrocu et al. 2013).

2.3 Knowledge Production Function to Investigate the Innovatory Effort by Public Research Investments

To understand how public funding influences knowledge production regarding cardiovascular devices, we based our analysis on the knowledge production function (KPF) framework developed by Griliches and Jaffe (Jaffe 1989, Grillitsch, Asheim 2018).

$$K_r = f(R_r, Z_r) \tag{1}$$

K_r refers to knowledge production in terms of innovative output in region r that is a function of two inputs. R_r is the innovatory effort of region r based on the endogenous growth model, which implies that production output is a function of endogenous (regional) factors (Furman et al. 2002). Z_r are additional regional indicators of this same region, such as the economic and financial capacity.

To measure knowledge production K_r, we rely on a bibliometric measure of innovation by capturing the number of publications in the field of cardiovascular devices. Although literature-based innovation measures were initially preferred as direct measures, most previous approaches have captured knowledge production by either R&D inputs or patents (Acs et al. 2002, Acs, Audretsch 1993, Coombs et al. 1996). R&D investments represent allocated investments but not necessarily innovation and must be considered inputs instead of outputs (Pavitt et al. 1987). Patents reflect the state of the invention but do not necessarily reflect the innovation it perpetuates as it continues to develop and diffuse. Patents, also, cannot capture innovation arising from daily practices that are often not patented (Pakes, Griliches 1980, Acs, Audretsch 1993). Since innovative activities of cardiovascular devices involve physicians in both pre- and post-launch phases, we rely on publications to capture the innovative activities most likely expressed in terms of clinical studies, scientific guidelines, or case reports. It is reflected by the globally increased number of publications in cardiovascular research, with Europe having outpaced the US and China in the 1990s and 2000s (Gal et al. 2017).

We considered innovatory effort R_r as the regional level research investments as funding received by the EU Framework 7 and EU Horizon 2020 programs. Previous studies have empirically identified positive effects of financing mechanisms (mostly, as the share of internal R&D) or human capital on the knowledge output of regions (Gumbau-Albert, Maudos 2009, Charlot et al. 2015, Tappeiner et al. 2008). Public funding is an important type of investment in research because it is pre-investment, similar to venture capital investment, in which future outcomes are yet unclear. An advantage of using public funding by EU programs is that it can be traced to the regions receiving it. We also account for variation in private investments by the number of clinical trials receiving sponsorship from private companies in our empirical approach.

3 Data and Methods

To empirically analyze the impact of research investments on knowledge output, we composed a cross-sectional data set of innovation activity in the years 2014–2017 by linking multiple data sources. Our investigation covered 27 EU member countries as of September 2020 plus the UK, Switzerland, Iceland, and Norway, summing up to a list of 31 countries[1]. In the final data set, all the data was uniquely assigned and aggregated to the level of 1,394 regions defined by NUTS-3. We then implemented an empirical strategy that accounts for potential confounding on the effects of funding mechanisms on knowledge output by considering additional regional characteristics and spatial dependency across neighboring regions as additional inputs to the knowledge production function.

3.1 Data Sources

To capture variations in knowledge output measured by publication activity due to investments in research and regional environment according to their corresponding regions, we extracted data from seven different sources [Supplement 1 – Source Data]. We collected bibliometric data from the US NLM MEDLINE/PubMed baseline database as the primary data source. It contains 26 million and 30 million publication records from MEDLINE and PubMed, respectively (Amelung 2017). We relied on the 2018 version of the baseline database that provides 4,374,797 citation records that we obtained via bulk download (NLM 2020a,c).

Although the US NLM is from the US, it is the prime source for biomedical research globally. Journals not included in the PubMed/Medline possibly do not meet the quality standards set by the US NLM (NLM 2021). Our captured publications, therefore, ensure that the knowledge generated is incremental. We further ensure that the coverage of Europe-origin journals is high, given that Europe-based authors may prefer to publish in them. Using the SCImago Journal & Country Rank database that lists 173 journals in cardiology and cardiovascular medicine with publishing offices in EU-28 countries, we found 141 journals (i.e., 81%) included in the PubMed/Medline baseline database as of 2021. The other 19% may not have met PubMed/Medline's quality standards.

To select relevant records from MEDLINE/PubMed, we used NLM's thesaurus classification of Medical Subject Headings (MeSH). The MeSH terms are NLM's in-house developed keywords for cataloging each publication depending on its subject matter (NLM 2019a). MeSH terms are assigned to each publication by a team of indexers who systematically scan the title, abstract, and publication. The MeSH classification is provided by a hierarchical tree structure containing 16 main branches, including diseases, drugs, therapeutic equipment, and processes, and each branch contains hierarchical sub-branches[2] In addition to its definition, each MeSH is described by a "DescriptorName" for one word/phrase description and is accompanied by "DescriptorUI", a unique ID number for that particular MeSH (NLM 2019b). Per publication, multiple MeSH terms may be assigned (NLM 2020b). We relied on the 2019 version of the MeSH tree.

Third, we used the U.S. Food and Drug Administration's (FDA) Product Code Classification Database to classify cardiovascular devices (FDA 2018). Most importantly, this database provides generic definitions of a set of approved medical devices by disease indication and the typical classification of medical devices by their risk. Fourth, we collected gross domestic product (GDP) per region for the years of 2014 to 2017 from Eurostat (Eurostat 2020) and national statistical offices in Switzerland (BFS 2019) and Iceland (Statistics Iceland 2019). Fifth, we obtained data on research funding received under EU Framework 7 and Horizon 2020 program at regional level as provided by the official online dashboard of the European Commission (European Commission 2020b).

[1] Liechtenstein was excluded from the dataset as no publications were recorded on cardiovascular devices.

[2] For example, the main branch "Analytical, Diagnostic and Therapeutic Techniques, and Equipment" includes "Surgical Procedures, Operative" as a sub-branch containing additional sub-branches such as "Cardiovascular Surgical Procedures" that has "Heart Valve Prosthesis Implantation" as a sub-branch that in turn has "Transcatheter Aortic Valve Replacement."

Sixth, we collected data about funding status of registered clinical trials reported in the extracted publications from the database provided by ClinicalTrials.gov (2021). Seventh, we collected additional characteristics of the region to account for health system related factors in a subset of four countries, relying on a publicly available previous data collected for these variables (Rabbe et al. 2021).

3.2 Classification of Publications of Cardiovascular Devices

We developed a programming algorithm to extract all publications from MEDLINE/PubMed that cover medical devices for cardiovascular diseases [Supplement 2 – Additional External Variables] [Supplement 3 – Program Code for Data Extraction and Preparation]. First, based on the MeSH tree, we classified publications as to whether they refer to medical devices in general. Second, we restricted the sample to publications with those MeSH terms for which we could attribute an approved medical device definition for a cardiovascular specialty by the U.S. FDA. Although our study focused on Europe, we relied on the classification of medical devices provided by the FDA because the recently published European medical device nomenclature was under development at the time of data-collection (European Commission 2020a).

To focus on publications about medical devices, using the MeSH tree, we included all MeSH terms that cover analytical, diagnostic, and therapeutic techniques and equipment [Supplement 4 – Auxiliary Data Created]. Specifically, we selected all the MeSH terms of the sub-branches E01 (diagnosis), E02 (therapeutics), E04 (surgical procedures, operative), E06 (dentistry), and E07 (equipment and supplies), with 2,178 unique MeSH terms in total.

To retain publications on medical devices explicitly for use in cardiovascular disease, as a second step, we mapped the identified MeSH terms with cardiovascular devices authorized by the U.S. FDA's Product Code Classification Database (FDA 2018). In this way, we ensured that the selected publications are linked to the FDA approved products to maintain our focus on those that succeeded the approval process (Stern 2017). The U.S. FDA medical device classification is based on risks posed by the devices on patients, I being the lowest and III being the highest risk. In the Product Code Classification Database, we selected all product definitions attributed to cardiovascular disease (medical specialty "CV"). To focus on devices that are likely part of cardiovascular interventions and avoid devices that mostly contain accessories to support interventions, we excluded class I devices, which includes devices such as forceps and scissors, for example. We included all 276 devices with moderate (class II, for example, cardiovascular blood flow meter) and greatest risk (class III, for example, pacemaker/cardiac resynchronization therapy) to patients (FDA 2017). The mapping exercise left us with 86 MeSH terms [Supplement 4 – Auxiliary Data Created].

3.3 Assigning Publication Geolocations to Identify Regional Innovation Systems and Knowledge Output

In total, we extracted data on 123,487 publications that we could assign to at least one MeSH term relating to a cardiovascular device and to a geocode in Europe [Supplement 4 – Auxiliary Data Created]. To obtain the geographical distribution of the publications of cardiovascular devices, we used the publicly available tool MapAffil to assign geocodes (latitudes and longitudes) to each publication based on the authors' affiliations (Torvik 2015). MapAffil is capable of correctly identifying 97.7% of the geolocation of a city reported in the author's affiliation variable provided by PubMed.

We restricted our analysis to publications published between 2014 and 2017 because MEDLINE/PubMed's indexing method started in 2014 to include information about affiliations of multiple authors (NLM 2019b). We assumed that not accounting for authors and their location beyond the first authors would heavily underestimate regional contribution to the knowledge output. Medical device research is often performed in networks of authors from different locations. In 2012, 40% of studies reported authors from two or more countries (Gal et al. 2017). Based on the assigned geocodes, we aggregated publications by regional level.

To identify distinguished regions in the RIS of knowledge production of cardiovascular devices, we relied on the geographical classification of regions defined by the Nomenclature of Territorial Units for Statistics (NUTS), provided by Eurostat and the Organisation for Economic Co-operation and Development (OECD) (Damanpour, Schneider 2009, OECD 2005). NUTS is a hierarchical geographical classification based on regional administrative structures of countries and territories to perform socio-economic and statistical analysis. Across all analyses, we used the 2016 version of the NUTS classification at the lowest level 3 as it refers to small regions for diagnosis of specific questions (Damanpour, Schneider 2009).

We distributed the geocodes of multiple affiliations of the same publication by equal weight. For example, a publication with three authors referring to geolocations in Milan, Munich, and Zurich was assigned three sets of geocodes corresponding to each of these cities. If the publication included authors from outside Europe, we discarded the affiliations from outside Europe to focus on innovation output located in Europe.

Data extraction was performed using SAS Enterprise Guide 9.4 (SAS Institute, Cary, NC, USA). Statistical analysis was performed using R, version 4.0.2. All program codes to extract and analyze all data sources and the data set for analysis are provided via the Open Science Framework (OSF) repository.

3.4 Empirical Knowledge Production Function Model

The aim of our empirical strategy was to quantify the effect of research investments on knowledge production measured by the number of publications assigned to one region, accounting for potential confounding of other characteristics of the region as a secondary input to knowledge production, and spatial dependency across regions. Considering the specification of the KPF as stated by equation (1), we specified the following linear regression model:

$$K_r = \hat{\beta}_1 X_r + \hat{\beta}_2 Z_r + \epsilon_r \tag{2}$$

K_r refers to knowledge output (number of publications) of region r. X_r is our variable of interest and captures innovatory effort of region r. Z_r represents characteristics of the region r itself that are reflected by suitable regional indicators. In our case, we captured economic performance by considering the GDP of that region. ϵ_r captures the error term. For all input and output variables, we provided specifications per capita by dividing absolute values by the number of inhabitants in the region. The estimate of $\hat{\beta}_1$ captures the effectiveness of innovatory effort by two types of measures. Our primary measure of innovatory effort is the monetary volume of funding received in the region via the 7th EU framework programme (FP7). It was rolled out from 2007 to 2013 as part of European Commission's research and innovation funding promotion to boost economic growth in the European Union. The program offers financial aid to EU member countries and a list of associated countries, including all countries in our analysis, and, subsequently, research activities taking place in those countries eligible for it (European Commission 2020c). It is the largest framework program for promoting research and innovation across Europe. Controlling for other factors of the region Z_r, we hypothesize that innovatory effort made through FP7 causes knowledge production between 2014 and 2017 to increase. In addition, we include a separate variable for its successor EU Horizon 2020, spanning from 2014 to 2020 (European Commission 2020d). That way, we account for lags of innovatory effort and hypothesize that higher current innovatory effort is associated with higher levels of knowledge production. In addition, we accounted for country fixed effects to compare estimates with and without heterogeneity that may persist due to first and second nature advantages between national environments. First nature advantages relate to geography of the region while second nature advantages relate to agglomeration economies that have advantages due to proximity of customers and suppliers, technological externalities and better matching between employers and employees (Charlot et al. 2015).

To account for other factors of the region that define knowledge output, we considered GDP in region r for the years 2014 to 2017 such that $\hat{\beta}_2$ is the estimate of the effectiveness of other characteristics of the region as input to the KPF. To provide a uniform measure of GDP, values were obtained at current market prices by million Euro, or other applicable local currencies, and converted to units of per million US Dollars by dividing them with purchasing power parities obtained using data provided by the OECD (2020b). We calculated averages to receive one mean and uniform GDP value for the period 2014–2017.

Finally, to account for proximity effects in innovatory effort and other characteristics of the region, we considered the spatial dependency of neighboring regions, assuming that knowledge production is not only influenced by the inputs of the KPF of the region itself but also by the inputs of the neighboring regions (Moreno et al. 2005, Charlot et al. 2015). We consider spatial proximity and the related correlations of dependent and independent variables as important given the role of user-producer interactions in the development process of medical devices and the fragmented nature of the medical device industry across geographical regions. Most importantly, we do not account for any collaborating clusters across neighboring regions ex-ante in our data, so we need to allow for knowledge and innovatory efforts to flow not only locally, but also across neighboring regions. Accordingly, equation (2) can be extended to a spatial form as follows:

$$\begin{aligned} K_r &= \hat{\rho}\,\boldsymbol{WK} + \hat{\beta}_1 X_r + \hat{\theta}_1 \boldsymbol{WX} + \hat{\beta}_2 Z_r + \hat{\theta}_2 \boldsymbol{WZ} + u \\ u &= \hat{\lambda}\,\boldsymbol{Wu} + \epsilon_r \end{aligned} \tag{3}$$

Spatial lags of these variables are denoted by $\boldsymbol{WK}$ referring to knowledge outputs of the neighboring regions, $\boldsymbol{WX}$ to funding mechanism received by the neighbor regions, $\boldsymbol{WZ}$ to GDP of the neighbor regions, and $\boldsymbol{Wu}$ to unobserved environmental characteristics of the neighbor regions. $\boldsymbol{W}$ is the weight matrix of the neighboring regions, for which we defined a contiguity neighborhood matrix that assigns equal weight to all neighbors with row-standardized values (Tosetti et al. 2018).

To assess the degree of spatial dependency across data reporting knowledge production and research investments across regions, we first performed Moran's I test for our specified models (Lesage 2008, Elhorst 2010, Tosetti et al. 2018). We accounted for the spatial dependency of both dependent and independent variables (Manski 1993): endogenous interaction by knowledge output in the number of publications of neighboring regions (ρ), exogenous interaction by inputs to the knowledge production function of the neighboring regions (θ), and correlated effects by unobserved environment of the neighboring regions (λ) (Elhorst 2010, Floach, Le Saout 2018). We followed a combined approach which included parts of both bottom-up and top-down approaches for the selection of order of spatial effects proposed (Elhorst 2010, Floach, Le Saout 2018). The purpose of the approach is to account for spatial lags of the dependent variable and the error term with robust Lagrange multiplier tests as a first step. As the second step, we specified a Durbin model, which refers to the baseline model as described in (3), including lags of independent variables and either ρ or λ. We then performed a likelihood ratio test, comparing the model specifications with and without spatial autocorrelation of the independent variables (θ) (Floach, Le Saout 2018). We only report relevant type of spatial model specified in case where spatial effects were confirmed. All spatial tests and analyses were performed using R version 4.0.2 (packages spdep, SDraw, spatialreg, rgeos) [Supplement 5: Spatial Analysis and Results].

To estimate the elasticity of innovatory effort and other characteristics of the region, we estimated models at the log scale (Moreno et al. 2005, Gumbau-Albert, Maudos 2009). Here, we needed to account for regions that do not report EU Horizon 2020 or FP7 funding. Estimating models at the log scale is particularly challenging for values of zero; we explicitly accounted for the lack of innovatory effort by including a dummy variable (Battese 1997). In the appendix (Tables A.1 and A.2), we report another version of the spatial KPF that excluded regions with zero innovatory effort in terms of public funding received.

3.5 Robustness analyses by input and output variables

To assess whether our results hold across different specifications, we performed additional analyses accounting for non-public innovatory efforts to fund randomized clinical trials that were part of the publications, the number of grants reported in the publications as innovatory efforts, and observed healthcare system-related factors of the region besides GDP.

To account for regional variation of innovatory effort from private sources, we measured receipts of private funding by capturing sponsorship of clinical trials by the industry. We relied on the reporting of clinical trials in the publications captured in the MEDLINE/PubMed database[3] to link them with sponsorship information in ClinicalTrials.gov (2021). In total, 1,242 clinical trials were reported in the publications. Accounting for both lead and collaborative sponsors types that include industry, government, and non-governmental agencies, we created a binary variable – "private funding." For publications corresponding to clinical trials with sponsorship from at least one industry sponsor, "one" was assigned, otherwise "zero." We counted the number of publications reporting private funding by region.

To account for an alternative measure of innovatory effort from public funding sources, we replaced the measure of innovatory effort by public funding with the number of grants reported in the publications in the MEDLINE/PubMed dataset. We relied on the reported element "GrantList" corresponding to those articles for which the authors reported grant funding. It includes the name of the grant-funding agency along with additional grant identifying details (NLM 2019b). These funding agencies are part of the list maintained by the NLM and consist of US government health organizations, US non-governmental funding organizations, and non-US funding agencies/organizations (NLM 2019b). We created a binary variable, "grant received," coded as "one" for a publication that reported at least one grant-funding agency and "zero" for no reported grant funding. We grouped and aggregated the binary variable corresponding to the regions where the published work was performed; thus, calculating the total number of publications that received grants per region. This variable allows us to account for both public and non-public grants as reported by the authors, while the EU Horizon 2020 and FP7 funding volume allows us to account for public funds only. As this variable was collected only from published studies, the grant variable does not account for funds acquired that did not end up in publication.

We considered factors related to the regional health care environment to account for additional confounding of the elasticities of public funding by other regional factors. For cardiovascular care, potential confounders of public funding are the intensity of hospital care in the region. In addition, there may be regional variations in unmet medical needs, driving clinicians to develop new products and seek funding opportunities. In a subset covering 422 regions of four countries (Germany, Italy, Switzerland, and Hungary), we relied on a publicly available and recently extracted data set of hospital counts and life expectancy at NUTS-level 3 (Rabbe et al. 2021). We first separately specified the baseline model from equation (2) for these subsets of regions and then added hospital counts and life expectancy to control for the regional health care system environment.

4 Results

4.1 Exploratory Spatial Data Analysis

Of the 1,394 regions in the 31 countries that we considered, 1,051 (75%) regions were active in knowledge production as they had at least one cardiovascular device-related publication between 2014 and 2017. Figures 1a and 1b provide an overview of the exploratory spatial data analysis that demonstrates the regional variation in knowledge output by number of publications in multiple western and southern European countries. The figures depicting the remaining countries from our dataset are provided in the appendix.

[3] In MEDLINE / Pubmed, an element named "DataBankList" provides ClinicalTrials.gov identifier (i.e., NCT number) in cases when publication reports results of a clinical trial (NLM 2019b).

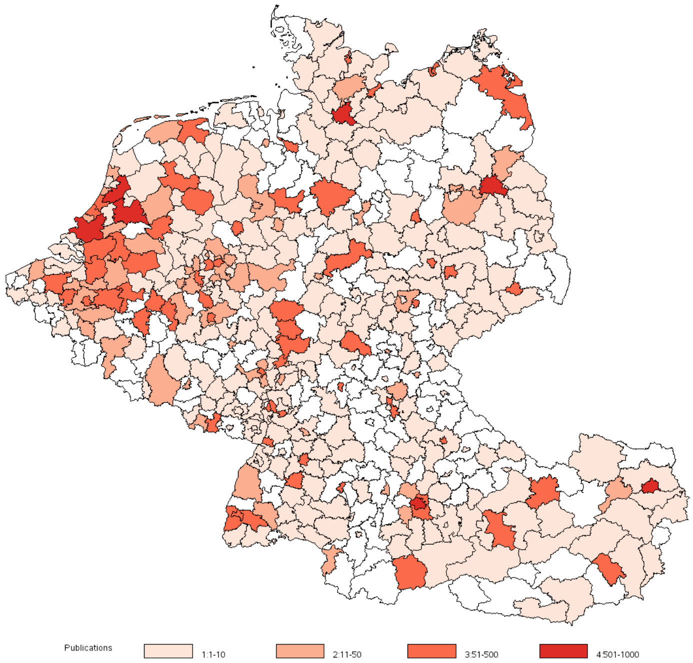

Figure 1a: Publication Output for Cardiovascluar Medical Devices at Regional levels of NUTS-3 in Europe: Netherlands, Belgium, Luxembourg, Germany, and Austria

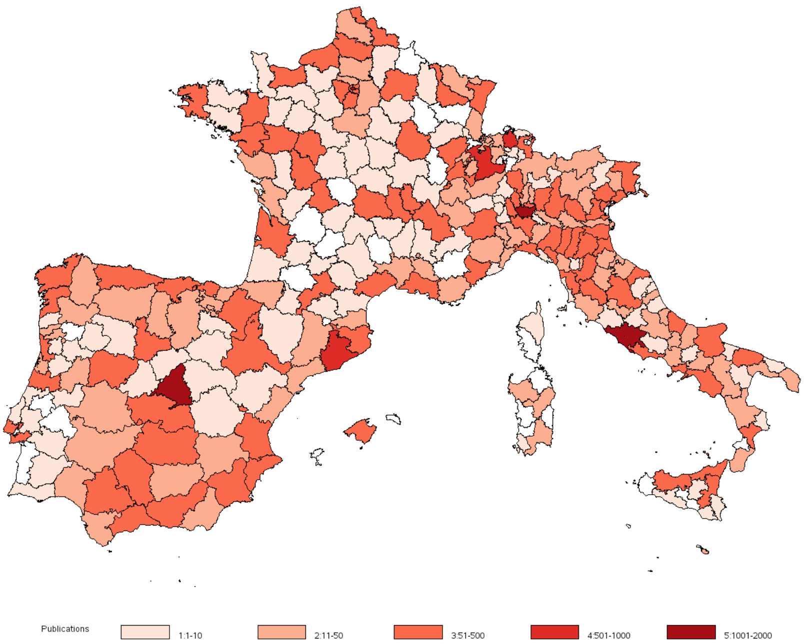

Figure 1b: Publication Output for Cardiovascluar Medical Devices at Regional levels of NUTS-3 in Europe: Switzerland, France, Portugal, Spain, Italy, and Malta

Table 1a: The ten Most Active Regions in Cardiovascular Device Knowledge Output by number of publications, 2014-2017

Region (NUTS-3)	No. of Publications	Share of Total Publications	EU 2020 Horizon Funding Volume in Million Euro	EU FP7 Funding Volume in Million Euro
Milano	1,730	2.58%	541	613
Westminster	1,674	2.50%	563	795
Paris	1,421	2.12%	2,558	3,168
Rome	1,380	2.06%	960	953
Madrid	1,195	1.78%	1,223	1,162
Barcelona	997	1.49%	1,023	1,005
Munich	911	1.36%	1,621	1,695
Groot-Amsterdam	905	1.35%	877	745
Groot-Rijnmond	828	1.24%	146	178
Berlin	812	1.21%	492	565

Note: Data on publications was obtained from the US NLM capturing 123,487 publications in the field of cardiovascular devices, 2014-2017. A region is defined by NUTS level 3.

Table 1b: The ten Most Active Regions in Cardiovascular Device Knowledge Output by number of publications per capita, 2014-2017

Region (NUTS-3)	Publications per Inhabitant	Share of Total Publications per Inhabitant	EU 2020 Horizon Funding Volume in Euro	EU FP7 Funding Volume in Euro
Westminster	709	5.36%	2,382	3,366
Erlangen	316	2.39%	625	725
Heidelberg	263	1.99%	1,854	2,342
Basel-Stadt	169	1.28%	620	998
Camden and City of London	152	1.15%	2,381	2,938
Jena	135	1.02%	460	481
Würzburg	134	1.01%	448	612
Freiburg im Breisgau	128	0.97%	254	69
El Hierro	121	0.92%	0	0
Regensburg	119	0.90%	220	424

Note: Data on publications was obtained from the US NLM capturing 123,487 publications in the field of cardiovascular devices, 2014-2017. A region is defined by NUTS level 3.

The descriptive analysis suggests that knowledge production is highly distributed across space (Table 1a and Table 1b). Even the region of Milano (Italy), producing the highest number of publications ($n = 1,730$), is responsible for only 2.58% of the total publication output of Europe. For the absolute number of publications, Italy (Milano, $n = 1,730$; Roma, $n = 1,380$), the United Kingdom (Westminster, $n = 1,674$), France (Paris, $n = 1,421$), and Spain (Madrid, $n = 1,195$) are the countries with the most active regions. For the number of publications per capita, the UK (Westminster, $n = 709$; Camden and City of London, $n = 152$), Germany (Erlangen, $n = 316$; Heidelberg, $n = 263$), and Switzerland (Basel, $n = 169$) were found to be the countries with the most active regions.

When we consider the country level, Germany ($n = 11,971$), Italy ($n = 10,250$), the UK ($n = 10,079$), France ($n = 7,302$), and the Netherlands ($n = 4,941$) are the most active countries (Table 2). The geographical span across the European Economic Area and adjacent countries further uncovers the regional level variation in knowledge production of cardiovascular devices. For example, Germany had the highest number of total publications ($n = 11,971$) whereas only two regions (Munich, $n = 911$; Berlin, $n = 812$) fell into the top ten highest publications producing regions, indicating that the knowledge production activity of cardiovascular device research in Germany is widespread rather than clustered in one or a few regions. On the contrary, Spain also has two

Table 2: Inputs and Outputs of the Knowledge Production Function of Cardiovascular Device Research by country, Europe 2014-2017

Country	Active Regions	Total Publi-cations	Publi-cations / Region	Publi-cations / Capita	H2020 funding (mill. €)	FP7 funding (mill. €)	No. of grants	No. of private funding
Germany	283	11,971	42	4,238	6,455	7,591	1,862	384
Italy	103	10,250	100	1,292	3,791	3,714	895	131
United Kingdom	164	10,079	61	2,728	5,846	8,020	6,122	191
France	86	7,302	85	644	4,997	5,832	545	174
Netherlands	37	4,941	134	702	3,431	3,847	1,188	158
Spain	53	4,920	93	582	4,100	3,468	422	129
Switzerland	21	2,673	127	503	1,408	2,500	341	64
Sweden	19	1,855	98	270	1,536	1,904	438	50
Denmark	10	1,813	181	292	1,151	1,095	222	55
Belgium	28	1,799	64	366	2,219	1,984	256	77
Poland	43	1,678	39	222	280	415	203	33
Greece	30	1,354	45	311	1,032	1,009	98	7
Austria	23	1,294	56	232	1,266	1,278	289	47
Portugal	20	824	41	109	701	540	71	4
Finland	17	758	45	176	1,013	904	361	20
Norway	17	756	44	160	1,007	789	113	22
Czech Republic	13	650	50	64	319	277	112	33
Ireland	8	508	64	68	501	640	118	4
Hungary	15	461	31	60	266	319	82	23
Romania	17	301	18	36	179	120	9	3
Croatia	11	167	15	38	64	71	1	0
Slovenia	8	147	18	35	236	157	11	1
Lithuania	5	99	20	15	56	46	0	3
Slovakia	6	97	16	15	83	68	22	1
Cyprus	1	71	71	8	212	100	32	0
Bulgaria	5	57	11	7	21	94	0	1
Latvia	2	51	26	8	67	44	8	7
Iceland	2	49	25	24	99	64	126	0
Estonia	2	28	14	7	93	93	2	2
Luxembourg	1	23	23	4	125	60	0	0
Malta	1	18	18	4	23	21	0	0

Note: Data on publications was obtained from the US NLM capturing 123,487 publications in the field of cardiovascular devices, 2014-2017. A region is defined by NUTS level 3.

regions, Madrid ($n = 1,195$) and Barcelona ($n = 997$), in the top ten absolute number of publication output, but it lags behind many other countries in terms of the total number of publications ($n = 4,920$), suggesting clustering of research only in very active centers. Table 2 further provides insights into country-level variations for the number of active regions (i.e., producing at least 1 cardiovascular device related publication), total publications, publications per region, publications per capita, total amount of EU Horizon 2020 and FP7 funding by million Euro, total number of publications reporting grants and private funding.

4.2 Estimates of the spatial Knowledge Production Function

The estimates of the (spatial) KPF models across the 1,051 regions reporting publication output suggest that innovatory effort in the form of EU FP7 program funding between 2007 and 2013 increases knowledge production of cardiovascular devices from 2014 to 2017. The elasticity was 0.40 ($p < 0.0001$). It declined to 0.36 ($p < 0.0001$) when we added country-fixed effects to the OLS specification and considered spatial dependency.

The EU Horizon 2020 program, that was active between 2014 and 2020, is positively related to knowledge production of cardiovascular devices, with an elasticity of 0.13–0.17 (Table 3). For the EU Horizon 2020 program, our OLS-based estimate of the elasticity was 0.17 ($p < 0.0001$). It declined to 0.13 ($p < 0.001$) when adding country-fixed effects and accounting for spatial dependency.

The estimates of spillovers generated by neighboring regions were reported as the indirect impacts of independent variables. Compared to the elasticity estimates in the focal region, these were negative and small, both for receiving funding from FP7 and EU

Table 3: Estimates of (Spatial) Knowledge Production Function by scientific publications per capita, considering funding from EU FP7 and EU Horizon 2020 program as innovatory effort – Inputs and outputs per capita (log-scale incl. zero)

	OLS	OLS	SAR
EU FP7 program	0.40***	0.36***	0.36***
	(0.04)	(0.04)	(0.04)
EU Horizon 2020 program	0.17***	0.13**	0.13*
	(0.04)	(0.04)	(0.04)
GDP	0.14***	0.86***	0.92***
	(0.03)	(0.13)	(0.13)
Spillover_FP7	-	-	-0.06
Spillover_Horizon2020	-	-	-0.02
Spillover_GDP	-	-	-0.16
Total_Impact_FP7	-	-	0.30
Total_Impact_Horizon2020	-	-	0.11
Total_Impact_GDP	-	-	0.77
Observations	1051	1051	1051
Country Fixed Effects	No	Yes	Yes
Adjusted R-squared	0.41	0.71	-
Moran's I	0.02	-0.03	-
LM test: lags of Y	1.34	14.01**	-
LM test: lags of e	0.76	2.43	-
ρ in SDEM (model with ρ and θ)	-	-0.15*	-
ρ in constrained SDM (model with ρ only)	-	-0.20***	-
LR test: lags of Y and X (ρ and θ)	-	50.17	-

Note: Data on cardiovascular device related publications in Europe from US NLM for the period 2014-2017. Outcome variable in each regression is the log value of number of publications per capita. GDP: gross domestic product; OLS: ordinary least squares; LM: Lagrange multiplier test; LR: likelihood ration test; SAR: Spatial Durbin Model; Y: dependent variable; ϵ: error term; ρ: estimate of spatial effect by dependent variable of the neighboring regions; θ: estimate of spatial effect by independent variables of the neighbor regions; λ: estimate of spatial effects by error variables of the neighboring regions. p-values: " $p < 0.05$, * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$.

Horizon 2020 (Table 3, column 3). In the assessment of the spatial dependency, Moran's I was insignificant. However, the Lagrange multiplier tests and their robust counterparts indicated possible interaction with knowledge outputs of neighboring regions (ρ). The likelihood ratio tests in the second step between SDM (model with ρ and θ) and its constrained form (model with ρ only) indicated the likelihood of only ρ to be present, leading to specification of a spatial auto-regression (SAR) model, often termed as a spatial lag model. Our estimate of the elasticity for the EU Horizon 2020 program remained at 0.13 ($p < 0.01$) in the SAR model. Considering that we capture fixed effects of all 31 countries to control for unobserved heterogeneity by the country, these elasticities are sizeable. The elasticities of GDP estimate in the KPF were at a range of 0.14–0.92. Here, we also find negative spillover of neighboring regions.

4.3 Estimates of the Knowledge Production Function controlling for additional inputs

Our estimates remain robust when considering additional inputs as confounders. As we cannot rule out that higher knowledge production has led to better funding opportunities of EU Horizon 2020 in the same period, only the estimates of EU FP7 can be validly interpreted as a causal effect of innovatory effort on knowledge production. When we additionally controlled for innovatory efforts by private funding for the clinical studies present in our dataset (Table 4, column 1), the estimate of the elasticity of the EU FP7 program reduced to 0.22 ($p < 0.0001$). These results demonstrate that even after controlling for private funding received by clinical trial sponsorship in our dataset, the effect of innovatory effort by EU FP7 program persists, although at a smaller magnitude.

Table 4: Estimates of (Spatial) Knowledge Production Function by scientific publications per capita, additional inputs by number of grants reported, private funding, health system related factors – Inputs and outputs per capita (log-scale incl. zero)

			4 countries Subgroup Analysis	
	OLS	OLS	OLS	OLS
EU FP7 program	0.22***	-	0.34***	0.34***
	(0.04)	-	(0.06)	(0.06)
EU Horizon 2020 program	0.08*	-	0.13'	0.14*
	(0.04)	-	(0.06)	(0.06)
Grants reported	-	0.49***	-	-
	-	(0.03)	-	-
Private Funding reported	0.49***	-	-	-
in clinical trials	(0.06)	-	-	-
GDP	0.54***	0.97***	1.26***	1.20***
	(0.11)	(0.10)	(0.20)	(0.20)
Number of Hospitals	-	-	-	0.55***
				(0.12)
Life Expectancy	-	-	-	-3.54***
				(4.88)
Observations	1051	1051	422	422
Country Fixed Effects	Yes	Yes	Yes	Yes
Adjusted R-squared	0.79	0.78	0.72	0.73
Moran's I	0.00	0.00	0.00	0.00
LM test: lags of Y	8.3*	5.94	0.59	0.19
LM test: lags of e	0.04	0.02	0.03	0.00

Note: Data on cardiovascular device related publications in Europe from US NLM for the period 2014-2017. Outcome variable in each regression is the log value of the number of publications per capita. GDP: gross domestic product, OLS: ordinary least squares, LM: Lagrange multiplier test, LR: likelihood ration test, SDM: Spatial Durbin Model; Y: dependent variable; ϵ: error term; ρ: estimate of spatial effect by dependent variable of the neighboring regions; θ: estimate of spatial effect by independent variables of the neighbor regions; λ: Estimate of spatial effects by error variables of the neighboring regions. p-values: ' $p < 0.05$, * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$.

When we consider innovatory effort by the number of grants reported in the context of cardiovascular device research (Table 4, column 2), we find a higher elasticity of 0.49 ($p < 0.0001$) as compared to our baseline models with the estimates of the EU FP7 and Horizon 2020 measures of innovatory effort. Considering other regional characteristics as additional inputs to the KPF with grants reported, we also find sizeable elasticity by the regional GDP at 0.97 ($p < 0.0001$).

Accounting for additional factors of the region that relate to the health care environment, we find similar estimates for the elasticities of the EU FP7 program in the subgroup of regions in Germany, Italy, Switzerland, and Hungary (Table 4, columns 3–4). At baseline, the elasticity of the EU FP7 program was 0.34 ($p < 0.0001$). When we controlled for the number of hospitals and life expectancy in the region, this estimate of elasticity remained the same at 0.34 ($p < 0.0001$) for the EU FP7 program.

5 Discussion

Our estimates of the (spatial) KPF for cardiovascular publication output in the 1,051 active regions across 31 European and adjacent countries suggest that innovatory effort via public funding substantially increases knowledge output. The estimates of the elasticities ranged between 0.36 and 0.40 for the EU FP7 program. The underlying (and considerable) heterogeneity in knowledge output that we documented is similar to the uneven distribution of medical device usage and companies across Europe (MedTech 2020a, Tarricone et al. 2017). We also uncovered small but negative spillover in innovatory effort and other characteristics of the neighboring regions on the regional knowledge production. We also find positive associations of 0.13–0.17 for the EU Horizon 2020 program, FP7's successor, although they cannot be interpreted as a causal effect of innovatory effort on knowledge production.

Contrary to our focus on cardiovascular devices that also has implications for patients receiving innovation faster, previous studies have identified the role of innovatory efforts by pooling input and output variables from several industries. The estimates of elasticities of knowledge output in these studies ranged from 0.24 to 0.90 (Moreno et al. 2005, Bottazzi, Peri 2003, Marrocu et al. 2013, Greunz 2003). Thus, our estimates of the elasticities for the FP7 funding (0.36-0.40) are in middle of this range. In their factorial analysis approach, Buesa et al. (2010) estimated the increase in the number of patents by about 400–1,100 due to a regional environment consisting of economic and human resources variables, about 200–270 due to innovatory firms' internal R&D investment, and about 25–80 due to the national economic environment. Some studies, such as Gumbau-Albert, Maudos (2009) and Charlot et al. (2015), estimated R&D elasticities on innovation outputs at 0.17–0.27 in Spanish and 0.26 in European regions, respectively; the associations we find for the EU Horizon 2020 funding are aligned more closely to this range (0.13–0.17). While these studies also capture innovatory effort by R&D investments, measurement variables differed as they capture R&D investments mainly by share of GDP or by internal R&D investment of the manufacturing firms. The relatively high elasticity for estimates of the FP7 funding program (0.36-0.40) is possibly due to a cumulative effect. Regions already receiving higher funding in the past had a higher potential of producing research activities resulting in publications 2014-2017.

Our estimates confirm that the public funding brought to a region has a considerable role in its innovation output in the medical device industry. For the medical device industry-specific evidence, several regional clusters have been described on a descriptive level, for example, the Medical Valley Nuremberg, Germany, or the Emilia Romagna region in Italy (Klein et al. 2015, Valley 2020). However, few studies focus on quantitative spatial analysis of the regions' inputs and outputs related to the medical device industry. The choice of innovation measure will also play an important role; analyzing elasticities of public funding may not have similar effects for early intervention measure such as patents that may predominantly rely on other funding sources such as venture capital. However, recent industry reports suggest that the European medical device industry, unlike that of the US, still heavily depends on public or semi-public grants (MedTech 2020b). In addition, even when private funding by the industry was controlled in case of some publications reporting clinical trials, the estimates of the elasticities of the EU FP7 program remained significant, albeit smaller.

The spatial spillovers of innovatory efforts on knowledge output are consistently negative, albeit on a small scale. It indicates that higher knowledge output in one region resulting from its regional innovatory efforts indirectly and negatively influences the knowledge output of neighboring regions. Innovative activity may withdraw innovative activity from neighbor regions. The small to non-significant estimates of spillovers that we detect are in line with previous evidence that uncovered the role of spatial proximity in knowledge production. While Moreno et al. (2005) has demonstrated that spillovers are significant for neighbors, as well as neighboring regions of the neighbors, Tappeiner et al. (2008) showed that spatial correlation did not exist after controlling for all traditional variables of the KPF. Finally, considering a semi-parametric approach, Charlot et al. (2015) demonstrated that spillover effects are significant only for certain thresholds of R&D expenditure.

The study had some limitations. First, our estimates of the elasticities of the KPF for the innovatory effort captured by EU Horizon 2020 program may be subject to reverse causality (Charlot et al. 2015). Most importantly, we cannot rule out that highly active regions in terms of publication output successfully attract more R&D resources in the form of grants or EU funding received. We aimed to accommodate this endogeneity issue by considering innovatory efforts provided by the EU FP7 program. Considering the estimates of the EU FP7 program, the threat of reverse causality is minimized as the publications we captured were published after regions could acquire funding for this program. In this way, we can rule out that the knowledge production we observe coincides with obtaining research funds from the same publication output. However, the regions that received more funding for EU FP7 may also contain more human resources in the academic activities that are more likely to attract public research funds in the first place. Thus, for EU Horizon 2020, we cannot fully separate the effects of receiving funding from the level of human resources dedicated to cardiovascular device research that are a prerequisite to attract funds. Previous studies have considered this type of endogeneity by capturing alumni representation in evaluation boards of funding institutions as an instrument of receiving grants (Payne, Siow 2003). Estimates of the applied instrumental variable regressions were similar in effect to those disregarding such type of endogeneity. Such data was not readily available at the European level in the context of this study.

Second, our funding measure by the number of grants reported in one of our robustness analyses may be subject to publication bias and bias if authors of one region would more actively report their grants than authors in another region. It would lead to a problem only in the case when there is a cultural practice in some regions for (not) reporting the grants with the publications compared to others.

Third, as we focus only on funding mechanisms as innovatory effort and GDP as a proxy for other regional characteristics, we cannot disentangle the relative elasticities of other types of innovatory efforts (most importantly internal R&D investments and human resources) and other regional economic or financial characteristics. For example, Buesa et al. (2010) identified the relative importance of multiple input factors in the KPF. Our primary aim was to evaluate the elasticities of public research funding relative to other inputs, such as regional characteristics. However, as GDP is the single-most-important indicator for economic activity of a region (OECD 2020a), one concern is that adding additional regional characteristics leads to biases in the estimate of the elasticity as these are intermediate variables on the path between GDP and publication output and may cause collider-stratification biases. Our subgroup analyses that include health system-related factors suggest that the estimates of the elasticities appear not strongly biased when we exclude additional factors related to innovatory effort.

Fourth, we exclude the regions for which no publication output was documented so that the estimated elasticities are conditional on some minimum degree of knowledge production. In our data, we find that the 472 regions that did not publish a cardiovascular device-related article received approximately 365 million Euro by EU FP7 funding compared to about 47 billion Euro received by the regions with at least one publication, that is about 1% of the total funding volume. Similarly, 588 million Euro in EU Horizon 2020 funding was received by these 472 regions, compared to 43 billion Euro in EU Horizon 2020 funding received by the regions with at least one publication – about 1% of the total funding volume. As documented earlier, innovation systems in the regions not generating knowledge output are likely very different from the other regions, such that our estimated elasticities may not be transferrable to these regions (Charlot et al. 2015).

Fifth, funding by EU Horizon 2020 and EU FP7 programs is targeted for multidisciplinary research. Therefore, the possibility of knowledge spillover from other technologies may moderate the effectiveness of the innovatory effort that we study for cardiovascular device related research only.

Our study provides implications for R&D policymakers as well as the industry. Given the high burden of disease in cardiovascular conditions, the global demand for R&D in cardiovascular research is high (Komajda et al. 2013). When considering promoting certain regions in their activity for knowledge production, most medical device innovators, especially SMEs, have already been relying on public funding to innovate (MedTech 2020b). We show that targeting the levels of innovatory effort in the form of providing funds does effectively increase knowledge production of a region and the underlying networks. This finding is also relevant to justify related health and R&D policies or non-profit initiatives that aim to improve the innovatory output of a region. While our results point to a large geospatial heterogeneity in access to novel treatments from medical device innovation, to what extent this innovatory effort leads to early adoption of new and effective technologies in daily clinical use needs further investigation. With such an analysis one could find out how much of the knowledge supported by public funded in a region benefits that region. This way, policy makers could assess the spatial rootedness of the knowledge production and thus, direct benefits to the region.

Our approach in extracting publications for a particular medical field and assign author affiliations may also be used to capture variation in knowledge production in other medical areas where user-producer interactions are important, and patents may not fully reflect the innovative activity beyond the first invention of the device. Location of knowledge production may also be linked to other regional level health-related variables such as mortality from cardiovascular diseases. This will allow studying, for example, whether having an innovating expert in the region would also lead to quicker adoption of health technology in routine care of cardiovascular patients and changes in the networks of these experts.

6 Conclusion

Knowledge production of cardiovascular devices is largely spread across the regions of Europe. Even the most active regions contribute relatively small shares of publications that document innovation in cardiovascular devices. Receiving funding as a form of innovatory effort is effective for generating new ideas and, subsequently, devices because large parts of the industry are organized in small and medium enterprises, which rely on the knowledge of clinicians and academics. Our results support the notion that the regional innovation systems in Europe can be fostered by public research investments to promote innovation in the medical device industry.

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A Appendix:

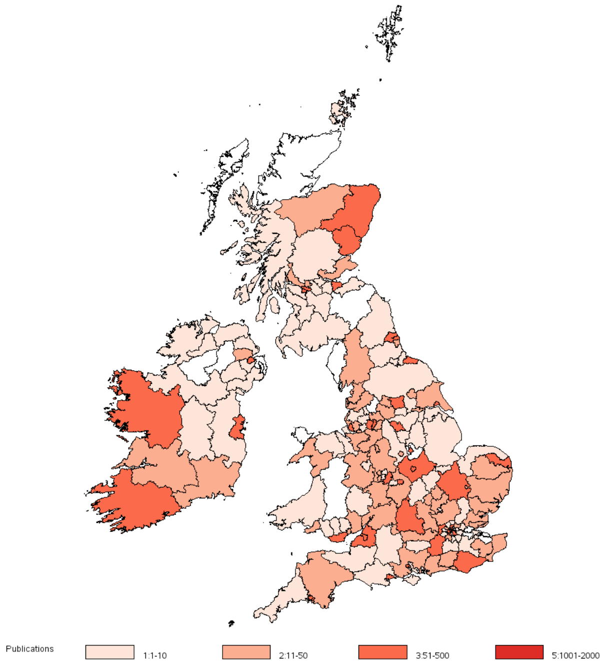

Figure A.1: Publication Output for Cardiovascluar Medical Devices at Regional levels of NUTS-3 in Europe: UK & Ireland

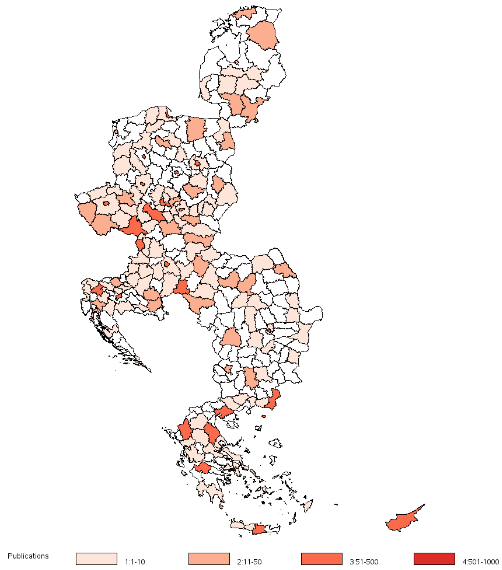

Figure A.2: Publication Output for Cardiovascluar Medical Devices at Regional levels of NUTS-3 in Europe: Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Croatia, Hungary, Lithuania, Latvia, Romania, Slovakia, Slovenia

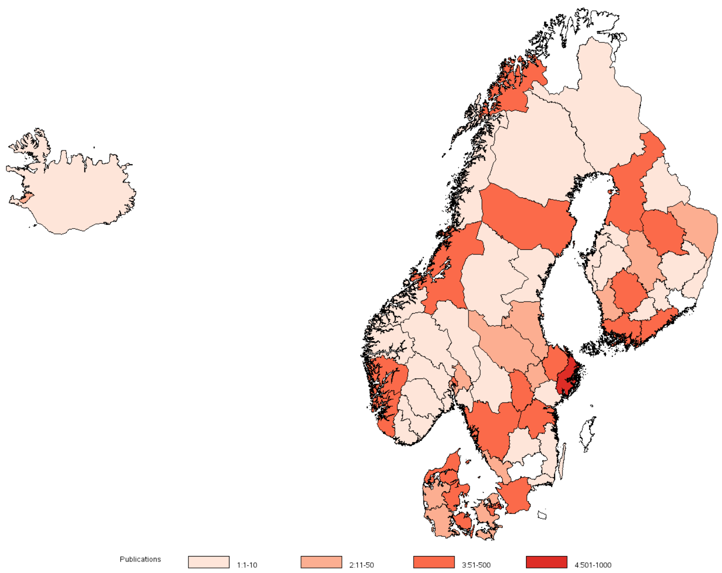

Figure A.3: Publication Output for Cardiovascluar Medical Devices at Regional levels of NUTS-3 in Europe: Iceland, Finland, Denmark, Sweden, Norway

Table A.1: Estimates of (Spatial) Knowledge Production Function by scientific publications per capita, excluding values with zero, considering funding from EU Horizon 2020 and EU FP7 program as innovatory effort – Inputs and outputs per capita (log-scale, excluding values with zero)

	OLS	OLS	SAR
EU FP7 program	0.41***	0.38***	0.37***
	(0.04)	(0.04)	(0.04)
EU Horizon 2020 program	0.17***	0.13**	0.13*
	(0.04)	(0.05)	(0.04)
GDP	0.10**	0.86***	0.92***
	(0.04)	(0.14)	(0.13)
Spillover_FP7	-	-	-0.07
Spillover_Horizon2020	-	-	-0.03
Spillover_GDP	-	-	-0.19
Total_Impact_Horizon2020	-	-	0.10
Total_Impact_FP7	-	-	0.30
Total_Impact_GDP	-	-	0.75
Observations	914	914	914
Country Fixed Effects	No	Yes	Yes
Adjusted R-squared	0.41	0.41	-
Moran's I	0.02	-0.04	-
LM test: lags of Y	1.35	3.3807	-
LM test: lags of e	1.20	17.90***	-
ρ in SDEM (model with ρ and θ)	-	-0.16*	-
ρ in constrained SDM (model with ρ only)	-	-0.24***	-
LR test of SDEM and SDM (ρ and θ)	-	52.62	-

Note: Data on cardiovascular device related publications in Europe from US NLM for the period 2014-2017. Outcome variable in each regression is the log value of number of publications per capita. GDP: gross domestic product; OLS: ordinary least squares; LM: Lagrange multiplier test; LR: likelihood ration test; SAR: Spatial Durbin Model; Y: dependent variable; ϵ: error term; ρ: estimate of spatial effect by dependent variable of the neighboring regions; θ: estimate of spatial effect by independent variables of the neighbor regions; λ: estimate of spatial effects by error variables of the neighboring regions. p-values: " $p < 0.05$, * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$.

Table A.2: Estimates of (Spatial) Knowledge Production Function by scientific publications per capita, additional inputs by number of grants reported, private funding, health system related factors – Inputs and outputs per capita (log-scale incl. zero)

			4 countries Subgroup Analysis	
	OLS	OLS	OLS	OLS
EU FP7 program	0.29***	-	0.35***	0.34***
	(0.06)	-	(0.07)	(0.07)
EU Horizon 2020 program	0.04	-	0.14	0.15*
	(0.06)	-	(0.07)	(0.07)
Grants reported	-	0.55***	-	-
		(0.03)		
Private Funding reported	0.57***	-	-	-
in clinical trials	(0.05)			
GDP	0.16	0.61***	1.08***	1.06***
	(0.15)	(0.13)	(0.22)	(0.22)
Number of Hospitals	-	-	-	0.62***
				(0.14)
Life Expectancy	-	-	-	-2.74
				(5.22)
Observations	321	393	354	354
Country Fixed Effects	Yes	Yes	Yes	Yes
Adjusted R-squared	0.94	0.92	0.74	0.48
Moran's I	-0.01	-0.04	0.00	0.01
LM test: lags of Y	1.33	4.67	1.18	0.36
LM test: lags of e	0.04	1.49	0.01	0.04

Note: Data on cardiovascular device related publications in Europe from US NLM for the period 2014-2017. Outcome variable in each regression is the log value of the number of publications per capita. GDP: gross domestic product, OLS: ordinary least squares, LM: Lagrange multiplier test, LR: likelihood ration test, SDM: Spatial Durbin Model; Y: dependent variable; ϵ: error term; ρ: estimate of spatial effect by dependent variable of the neighboring regions; θ: estimate of spatial effect by independent variables of the neighbor regions; λ: Estimate of spatial effects by error variables of the neighboring regions. p-values: " $p < 0.05$, * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$.