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Biomarker adoption in developmental science: A data-driven modelling of trends from 90 biomarkers across 20 years

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Abstract

Developmental scientists have adopted numerous biomarkers in their research to better understand the biological underpinnings of development, environmental exposures, and variation in long-term health. Yet, adoption patterns merit investigation given the substantial resources used to collect, analyse, and train to use biomarkers in research with infants and children. We document trends in use of 90 biomarkers between 2000 and 2020 from approximately 430,000 publications indexed by the Web of Science. We provide a tool for researchers to examine each of these biomarkers individually using a data-driven approach to estimate the biomarker growth trajectory based on yearly publication number, publication growth rate, number of author affiliations, National Institutes of Health dedicated funding resources, journal impact factor, and years since the first publication. Results indicate that most biomarkers fit a "learning curve" trajectory (i.e., experience rapid growth followed by a plateau), though a small subset decline in use over time.

KEYWORDS
biomarkers, developmental psychology, developmental science, metascience

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1 | INTRODUCTION

The integration of biological data into child development research, from measures of hormone levels to brain structure to molecular measures, such as deoxyribonucleic acid (DNA) and epigenetics, has been used to examine biological mechanisms, precursors to disease, residues of exposure, and moderators of response (Harris & Schorpp, 2018; Lenzenweger, 2013; Lerner, 2012; Mitchell et al., 2016). Scholars who study child and human development have been trying to integrate biological theory, methods, and data for centuries (Bernard, 2012; Meloni, 2014, 2016). Early theories of social processes were squarely rooted in Darwin's theory of evolution (Thornton, 2005), and today scholars use biomarkers to better understand the interplay of multiple levels of analysis using frameworks, such as bioecological systems theory, developmental psychology, Research Domain Criteria (RDoC), etc. (Insel et al., 2010; Lenzenweger, 2013; Lerner, 2012). Often, biology provides great insights into social processes, but it has also run amuck with disastrous effects (e.g., phrenology, eugenics; Meloni, 2016; Thornton, 2005).

Since the late 20th century, there has been a rapid integration of measures of biology into developmental research, in part due to the rapid technological advancements that afforded these measurements (Freese et al., 2003; Harris & Schorpp, 2018; Justice et al., 2018; Kaplan & Wong, 2011; Mitchell et al., 2016). Several rationales have been provided for integrating biomarkers with social and behavioural data (Falk et al., 2013; Meloni, 2016; Mitchell et al., 2013). For most developmental outcomes, biology is expected to be a mechanism linking social (and other) exposures to development. Also, of particular interest to developmental scientists, biomarkers could be used as indicators of exposure, so that, even if they are not part of the causal pathway from external stimuli to outcome, researchers can reconstruct the (sometimes unobserved) past. Similarly, many biomarkers were developed to indicate disease before typical symptoms emerge (Falk et al., 2013; Justice et al., 2018; Martin et al., 2019; Mitchell et al., 2016; Singh & Rose, 2009). For others, even if the biomarker was not part of the causal pathway from the primary explanatory variable to the outcome, the inclusion of biomarkers may improve the primary association estimate (i.e., using the biomarker as a covariate). In addition to these more scientific reasons, others have suggested that the prominence of biology as a scientific field has led to its integration into less prestigious areas of science to improve the scientific reputation of practitioners (Bernard, 2012).

Yet, most biomarkers were not developed with the goal of examining variation related to social behaviour, to study mechanisms linking the environment to child development outcomes, or to be measured outside of a lab or clinic. Furthermore, most were not developed with children as the target (Justice et al., 2018; Meloni, 2016; Mitchell et al., 2016; Singh & Rose, 2009). Attempts to identify biomarkers relevant to developmental stage, consequences of exposures, and health outcomes have been widely embraced by developmental scientists. However, whether a biomarker will be useful for a field is often difficult to determine, particularly for scholars with no or limited advanced training in biology. Small samples (Davis-Kean & Ellis, 2019; Ritchie, 2020) and incorrect interpretation of biomarkers (for an example of this discussion with DNA methylation, see Moore & Kobor, 2020; Ritchie, 2020) are regularly observed as limits to accuracy in most studies of infants and children, and likely contribute to a replication crisis. Importantly, some biomarkers also fail to live up to their initial promise.

In this paper, we document the patterns of adoption and use of biological metrics in relation to developmental science. Developmental science is an interdisciplinary field that draws from psychology, biology, and sociology to describe and understand aspects of human development (Bronfenbrenner & Evans, 2000). Though the field does not focus on a specific period of development, many researchers in developmental science study the period from prenatal development to adolescence given the rapid changes occurring in brain and behavioural functioning in the first two decades of life (Lenroot & Giedd, 2006; Tierney & Nelson, 2009). Although there is nothing theorized about models of biomarker integration specifically into developmental sciences, the effects of novel findings and technical innovations (i.e., new data, new statistical technique, and unique finding) have been considered as influencing other fields or markets (Fenn, 1995; Fenn & Linden, 2003; O'Leary, 2008; Ritchie, 2020). For example, innovative technologies are thought to emerge and change as part of a hype curve or cycle. This hype curve is thought to have five general stages (see Figure 1a; Fenn & Raskino, 2008): 1) the technology trigger phase when the technology growth is

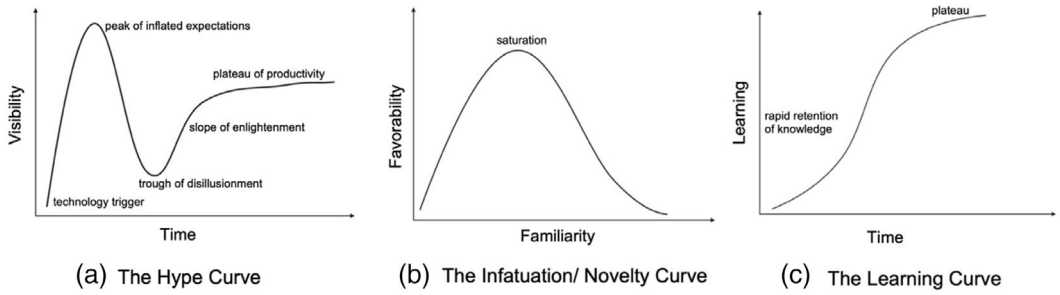

FIGURE 1 Potential patterns of adoption and use. *Note*. Figure created with BioRender.com based on prior research (Adler & Clark, 1991; Baloff, 1966; Berlyne, 1970; Fenn & Raskino, 2008).

driven by the potential of the innovation; 2) the peak of inflated expectations phase when several initial success stories are publicized but access to the technology is still limited; 3) the trough of disillusionment when the hype rapidly declines due to realistic re-adjustment of the innovation's potential impact; 4) the slope of enlightenment, a long phase in which an often small group of cautious users remain attentive to how the innovation is appropriately used; and 5) the plateau of productivity in which the true advancement in the broader field can take place. More broadly, though, social and developmental sciences have had a long history of attempting to examine how scientific methods and ideas spread through a field. Two very prominent social psychological theories that might apply are the infatuation/novelty curve and the learning curve. The infatuation or novelty curve (see Figure 1b) was first proposed in 1968 and generally suggests that as familiarity grows, so does favorability until saturation is reached and then begins to decline (Berlyne, 1970). The learning curve (see Figure 1c) is even older (1924), and is essentially a cumulative density function related to knowledge, such that more rapid retention of knowledge occurs at the beginning, slowing over time until it becomes flat toward the end (Adler & Clark, 1991; Baloff, 1966). Some have suggested that the innovative technology hype curve is just the combination of an infatuation curve with a slower learning curve following it, so that the real growth comes after a bout of infatuation (Dedehayir & Steinert, 2016). It is this potential insight into the underlying adaptation processes of developmental science to the innovation of a novel biomarker that may afford better understanding and thus more realistic expectations for current and future biomarkers.

The degree to which biomarkers follow a specific trend (hype curve, infatuation curve, and learning curve), allows us to document the growth in biomarker use and make inferences about patterns of adoption. Furthermore, this approach provides the opportunity to make predictions on future use of biomarkers. Our goals are to: (1) document historic patterns of biomarker use and (2) utilize those observations to offer a generalizable predictive model that can be applied to foreshadow future trends. To do this, we gathered publication related statistics for 90 biomarkers to create a set of content-agnostic predictive models that both explain and predict publication trends.

2 | METHOD

2.1 | Biomarker selection

In our modelling plan, each biomarker is the modelling unit in the analyses. Thus, our first step was to identify a list of biomarkers used in developmental science by searching consortia (EArly Genetics and Lifecourse Epidemiology [EaGLE], Early Growth Genetics, Telomere Research Network, Environmental Influences on Child Health Outcomes, etc.), large data sets (National Study of Adolescent to Adult Health, Fragile Families and Child Well Being, Adolescent Brain and Cognitive Development Study, etc.), and databases (not only those with child/adolescent samples), such as the Biomarker Network (https://gero.usc.edu/cbph/network/), and meta-analyses (Justice et al., 2018). Although this

was not a list of all potential biomarkers, it was intended to be large enough to derive sufficient data to generate a predictive algorithm. A round of screening of the original list of 95 biomarkers was conducted based on the availability of developmental publications on the Web of Science and National Institutes of Health (NIH) funding. Biomarkers with too few publication entries (less than 50 publications) or fewer than five NIH-funded projects were not retained for further analysis, leaving 90 biomarkers for the following stage of analysis. For the list of biomarkers and the number of publications and NIH funded projects, please see Table S1.

2.2 | Measures

The measures used in analyses of change in use of each biomarker include the number of publications, publication growth rate, number of author affiliations, number of projects funded by NIH, amount of funding given by NIH, journal impact factor, and years since first publication. A key aspect of reproducibility and future prediction is that these measures can be obtained and merged from publicly available sources for the 430,000 articles and 90 biomarkers. These statistics are by no means the only ones we think are relevant to predicting research trends. Nevertheless, they capture important information related to the publication activities for each biomarker.

A key concern for linking these data is to verify that the merging is done correctly for each biomarker. For example, all 430,000 articles had journals to be matched with impact factors. Similarly, each biomarker every year had a different publication count and NIH funding amount, and number of affiliations of institutions included. For each variable, the first and second authors co-developed the data query and processing workflow. During the workflow development process, these two authors together reviewed the output for each query and processing step to identify behaviours contradicting expectations, including checking the resulting data frame for illogical values as well as frequently visualizing the data to check for anomalies. The workflow was standardized and later applied to query each of the 90 biomarkers. Even with standardized processing, both authors examined the data frame entered into the analyses, as well as the results, to see if there were improbable results from edge cases not considered during the development stage: drastic changes in numbers, such as yearly growth rate of -1 or positive infinity due to biomarkers having no publications in some years, were manually corroborated to catch previously undetected programming errors. Possible errors in data gathering, such as double counting for variables like NIH funding data, were also monitored by the authors through sampling of the gathered data. All data searches used in the final analysis were conducted on December 31, 2020.

2.2.1 | Yearly publication number

The yearly number of publications is the primary dependent variable in our modelling process. We assert that sustained interest in biomarkers will be largely translated to the number of peer-reviewed publications and thus use the yearly publication number as the outcome variable of our modelling process. In addition to serving as the outcome variable, the publication numbers from previous years serve as important indicators to current research interest. For the purposes of this study, the yearly publication number includes only articles published in peer-reviewed journals, given that abstracts, presentations, working papers, dissertations, reviews, unpublished commentaries, and other types of reports were not able to be collected using standardized procedures.

We used the Web of Science to query publication information for each of the selected biomarkers. The Web of Science offers broad and consistent coverage of journal publications across various scientific disciplines, allowing us to capture the adoption of biomarkers in papers relevant to developmental science. The Web of Science offers comparable performance to other journal indexing databases, such as SCOPUS and Google Scholar for journal publications (Bergman, 2012; Martín-Martín et al., 2018). We decided against merging multiple databases after weighing the risk of formatting discrepancies across databases that can lead to double counting of publications against the

limited added benefit of adding comparable sources of journal publication data. For each biomarker, we used the following statement to query relevant publications within developmental science: "Text Search = (the query for each biomarker) AND (CHILD* OR ADOLESCENT* OR INFANT* OR NEWBORN* OR PEDIATRICS*)". All biomarker names were quoted in the search, to avoid partial matches to the biomarker names. All entries returned from the query were retained. Publication data after 2020 were removed due to incompleteness. Publications prior to 2000 were also removed, as we planned to focus on the time range where most of the included biomarkers had adequate publication data coverage across the modelling timespan. Between 2000 and 2020, among the 90 biomarkers, the annual number of publications ranged from 0 to 4635, with a median of 90 publications.

Considering changes in publication numbers across time requires including the potential influence of inflation in article publications. As seen in the Dimensions database, which tracks the overall publication numbers across years (https://app.dimensions.ai/discover/publication), the yearly number of all scientific publications increases over time (Bode et al., 2018). To make the number of publications comparable across years to model the ebb and flow in the research interest for each biomarker, the queried publication number for biomarkers in a given year was divided by the total scientific publication number of that year from the Dimensions database, which allows for instant tabulation of all publications for a given year after limiting the search to only journal publications, a feature that is not available in the Web of Science. We considered using total publications for developmental science as the denominator, but decided to use all articles instead in order to be comparable in approaches using publications and grant output.

2.2.2 | Publication growth rate

The growth rate of publications related to each biomarker for a given year captures the acceleration in publication interest. The rate of change for each year was defined as the percentage change in the rescaled publication number relative to the statistic from the previous year. Between 2000 and 2020, among the 90 biomarkers, the growth rate ranged between −89.2% and 966.8%, with a median of 1.6%. The detailed growth rate for each biomarker across years is included in Table S2.

2.2.3 | Number of affiliations

The number of affiliations involved in publications for each biomarker offers information on the penetration of a biomarker into the field. The number of affiliations is largely unrestricted except for the total number of existing research institutes, especially for biomarkers not requiring expensive and specialized assaying processes, thus allowing for rapid growth of research output related to particular biomarkers.

To tabulate the author affiliations that appeared in publications for a specific biomarker during a given year, we counted the number of unique affiliations among the publications gathered for our analysis from the Web of Science. Affiliations appearing multiple times for a biomarker were counted as one for that year, whereas 0 was assigned to the biomarker if no affiliation produced any publication that year. Between 2000 and 2020, among the 90 biomarkers, the yearly affiliation number ranged between 0 and 5962, with a median of 188 affiliations per biomarker per year.

2.2.4 | NIH funding

Funding provides critical support to research activities, especially for biomarker research that typically involves expensive collection and measurement processes. We are interested in both the total funding amount associated with each biomarker, as well as the number of funded projects. While the total funding amount made available to

specific biomarkers is an indicator of the resources supporting the research popularity, it may be accounted for by only a few large grants. Thus, we also included the number of projects funded to capture the spread of funding support that drives the popularity of specific biomarkers.

The number of NIH projects funded, as well as the monetary amount of funding from the NIH were used to approximate funding availability for each biomarker. We selected NIH due to the wide range of scientific disciplines it supports, as well as the number of grants it awards. NIH funding information for relevant projects was queried in the Research Portfolio Online Reporting Tools (RePORT) on the NIH website. The following query for NIH-funded projects was used: "Text Search: (the query for each biomarker) and (child or children or infant or newborn or pediatrics) (advanced)". The projects with the same project ID were merged together each year, with their total funding summed. Some projects had sub-projects, which created overlaps with parent projects. To solve this problem, sub-projects were included in our data only when their parent projects were excluded to prevent double-counting. All data after 2020 were removed due to incompleteness. Between 2000 and 2020, among the 90 biomarkers, the number of funded projects ranged from 0 to 2186, with a median of 21 projects funded by NIH.

Similar to publication increases, both the number of projects funded and the total amount of funds from NIH have increased across years, thus requiring adjustment to make the research resources available to biomarkers comparable across years. To do so, we obtained the yearly total number of projects funded by NIH, as well as the yearly sum of funding provided to all projects, to serve as denominators in the corresponding adjustments. The yearly total statistics were obtained from RePORT by querying all projects from a given year without supplying any search terms.

2.2.5 | Ranking of publication outlets

The increase in popularity for some biomarkers could be partially attributed to publications in journals with lower impact factors, as more researchers compete for similar work to be published in higher impact outlets. While the journal impact factor does not necessarily indicate something meaningful about the quality of journals or a given article published in that journal, this metric nevertheless reflects one method for assessing prestige within the scientific community. By including journal rankings to predict popularity, we tested if rapidly rising use co-occurs with a higher proportion of lower-ranked journal publications.

To evaluate the impact of journals, we used the SCImago Journal Rank indicator (SJR indicator). We used the total past 3-year citations for journals as the foundation for computing the journal impact factor. The SJR indicator assesses the impact of journals contained in the Scopus database yearly (Scimago Lab, 2022). The SJR indicator is available for journals between 1999 and 2020.

Each of the publications queried from our analysis was given a SJR indicator value through matching the journal name from the Web of Science query to the journals in the SJR database. However, 19% of all publications could not be given a SJR value because some journals queried from the Web of Science were not included in SJR in specific years. To solve this problem, a 0 was given as the SJR indicator for these publications, with the assumption that journals not included in the SJR database may not have established high impact, such as journals that were newly established. These publications were not assigned as missing to avoid the quality metric being biassed upward for biomarkers popular in journals without impact factors.

For our modelling approach, we used both the yearly average SJR across all publications on a specific biomarker and the yearly variance of the SJR indicator for publications on a biomarker. The yearly average captures the overall impact of biomarker research, whereas the variance captures the spread of the impact of specific biomarker research. Between 2000 and 2020, among the 90 biomarkers, the yearly average SJR ranged from 0 to 14,302, with a median of 1272; the yearly median SJR ranged from 0 to 14,302, with a median of 966; and the yearly variance in SJR ranged from 868,314 to 54,036,606, with a median of 1,540,092. SJR impact data was not rescaled in our analysis.

2.2.6 | Time since first adoption in developmental science

One final predictor was the number of years since a biomarker was first adopted in developmental science, as determined by the earliest publication indexed by Wed of Science from our search for the particular biomarker. Beyond understanding the general progression of popularity through time, we can also better capture the effect of other predictors included by controlling for the effect of time since first adoption. Among the 90 biomarkers, the number of years since biomarker adoption ranged from 0 to 115, with a median of 27.

2.3 | Biomarker trajectories descriptive analysis

Our descriptive analysis involves three parts. The first set of analyses offers a direct account of the changes in publication trends for each of the 90 biomarkers across time. Due to the number of individual trajectories involved, we cannot describe and interpret each trajectory. Instead, we present biomarker trajectories with two different exemplars of grouping and provide the data and an open-source application (ShinyApp; https://hypecurve.shinyapps.io/hypecurve/; more description in the results section) to facilitate more in-depth analyses. In the second part, we provide trajectory characterization analyses, which pull apart key aspects of the changes in individual biomarkers. In the third part of the descriptive analysis, we group the biomarkers conceptually, organizing them into five categories including: ageing measures, blood count measures, brain-based measures, common medical measures, and molecular measures. Although there is heterogeneity within each group and conceptual overlap between groups, showing clusters of measures provides some important insights not as easily seen in the individual analyses of the 90 biomarkers.

2.4 | Modelling trajectory associations

Predicting the yearly publication trends years into the future based on past publication statistics provides an opportunity to potentially assess how a biomarker might change (grow, decline, or plateau). To examine the potential to use publicly accessible data to predict biomarker trajectories, we propose two modelling frameworks: a polynomial multilevel model and a random forest model. Both models also identify the important driving forces behind publication trends. The ShinyApp (https://hypecurve.shinyapps.io/hypecurve/) provides estimates of both methods for future prediction.

2.4.1 | Polynomial multilevel model

The polynomial multilevel model offers a flexible approach to model trajectories by accounting for the effects of time and other predictors on publication trends while also modelling the dependency among data from different years for the same biomarker. Because of the dependencies in data, treating yearly observations for the same biomarker as independent would violate assumptions for linear regressions, thus warranting the use of multilevel models.

In formulating the multilevel model, each biomarker was chosen as a level 2 unit, while the yearly publication data for biomarkers formed the level 1 observations. To avoid the issue of multicollinearity, we did not include all possible predictors from 3 to 5 years ago as fixed effect predictors. For fixed effects, both a forward selection and a backward selection procedure were used to retain predictors that were shown to have yielded the largest decrease in the Akaike information criteria (AIC) and Bayesian information criteria (BIC) at each step. Both selection processes stopped when adding or leaving out any of the variables no longer yielded lower AIC and BIC. For random effects,

the random intercept and the random slope of year number were used to represent the different sizes and speeds of increases in publication numbers for different biomarkers.

Because some of our variables can be tiny in terms of absolute quantity, such as the very small number for the adjusted yearly publication number, some of the model coefficients would be extremely small, thus hindering our interpretation. Accordingly, to avoid very small coefficients in models while retaining the distributions of variables included, we used a min-max normalization process, which rescaled all the variables within a range between 0 and 1. In the polynomial multilevel model, the rescaling was conducted across all biomarkers rather than within each biomarker. The rationale was that the differences between magnitudes of data for biomarkers are readily accounted for by random intercepts and random slopes, leaving us to interpret the effects of predictors largely unaffected by the biomarker-specific effects.

2.4.2 | Random forest regression

Random forest regression has been widely used in modelling highly nonlinear and interactive relations among many predictors and a continuous outcome with high accuracy. The model averages the predictions from many decision trees, each containing some split decision point at which a random set of input variables are entered to yield a single variable that reduces the prediction error in the outcome variable the most. Each tree is trained with a random subset of the data. The decision tree structure quite exhaustively learns the relation between input variables and output variables, thus risking overfitting the model to the specific training dataset. The design of the random forest model promotes the generalizability of the learned model to other datasets with both the random input variable selection at decision points and the random data sub-setting in the training process, all the while using an ensemble of trees to average the prediction output. For our purpose of predicting publication interest with many predictors, as well as offering a generalizable model to other biomarkers not included in our dataset, random forest regression provides a good fit.

Random forest models also allow for some level of interpretability through computing the contribution of each input variable to the reduction of outcome variable prediction error. The relative contribution of each of the included predictors is called feature importance. We planned to use feature importance to interpret the random forest model, as well as to guide the formulation of a theory about publication trends.

For the predictors, we included the 1st to 4th power of year number, as well as the following variables from 3 to 5 years ago: yearly NIH grant project number, yearly total NIH funding amount, yearly NIH mean funding amount per project, yearly affiliation number, yearly growth rate of publication number, yearly mean SJR indicator, and yearly variance of SJR indicator. The outcome variable was the adjusted yearly publication interest. To reduce the impact of differences among biomarkers, min-max normalization was conducted on all covariates except year numbers and growth rates for each biomarker.

3 | RESULTS

3.1 | Descriptive data

In addition to providing a dataset of the 90 biomarkers for each of the 20 years (https://osf.io/ksj2n/), we created a visualization tool for charting the trends within developmental science research (https://hypecurve.shinyapps.io/hypecurve/). This ShinyApp allows for viewing a single trajectory or multiple trajectories at the same time by toggling the biomarker labels. Furthermore, because different biomarkers occupy distinctive ranges of publication trends, some biomarker trajectories will look flat based on the scaling used. The autoscale function (symbol: two lines with points on each end crossing) above the biomarker list will rescale the plot to

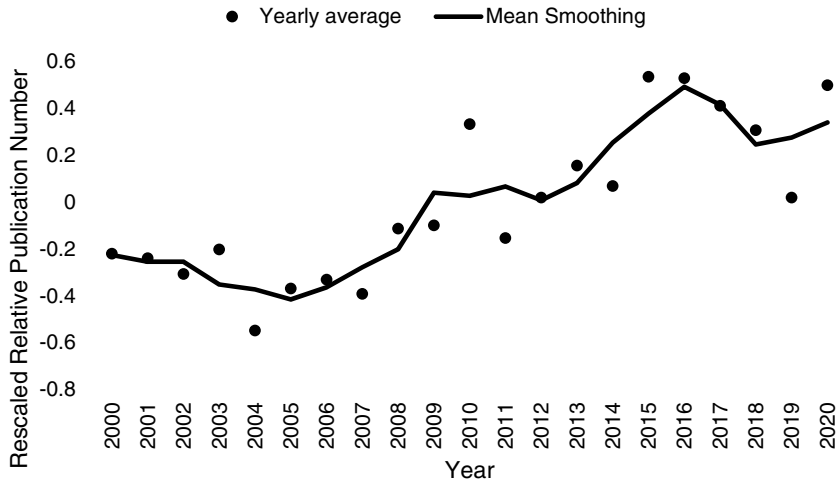

FIGURE 2 Average rescaled relative publication number with smoothing across all 90 biomarkers

show the real fluctuations in popularity across the year. More instructions for the use of the app are also available at the top of the app page.

The first part of the planned descriptive analysis, the plotting of the publication trends for all biomarkers, is presented in the first panel of the ShinyApp. Because plotting 90 biomarkers together creates many difficulties for interpretation, we first attempted to plot the overall growth trajectory of all the biomarkers. Because biomarkers have vastly different scales of publications, simply averaging the growth trajectory would heavily bias the overall trajectory toward biomarkers with relatively greater publications. To resolve this issue, we first rescaled the publication number within biomarkers before taking the yearly average of the rescaled publication number across all biomarkers. This way, each biomarker had equal representation in the overall trajectory. The overall trajectory aggregated from all biomarkers is shown in Figure 2. A smoothing technique (Jones & Roediger, 1995) was employed that accounts for the mean of adjacent point values. We observed a trajectory of faster early growth (compared to publications in general) followed by a slower change (typically a plateau or even a small decline relative to publications in general). This suggests that most biomarkers appear to follow a "learning curve" style growth (see later trajectory analyses).

For the biomarkers conforming to the learning curve, we have provided four biomarkers for illustrative purposes, seen in Figure 3. Like the rescale done for plotting the overall trajectory in Figure 2, the publication trends of biomarkers were rescaled within each biomarker to illustrate the shape of the trajectory rather than focus on the large differences in total publication. However, some biomarkers, such as the serotonin transporter gene (5-HTT) and transforming growth factor β (TGF-β), have growth curves that are unusual relative to other biomarkers and more akin to an infatuation or hype curve with rapid growth and a similarly rapid decline in publications. There are additional biomarkers that appear to have been in gradual decline since the beginning of our sampling frame, such as lymphocyte count and carbon dioxide (CO_2). Four examples of such trajectories are included in Figure 4, with the publication trends rescaled within biomarkers to aid comparisons while preserving the shape of the trajectories.

3.2 | Trajectory characterization analysis

The second part of the descriptive analysis is the trajectory characterization analysis, which was designed to offer an intuitive view into changes in biomarker publications. With a set of multiple linear regressions with only time since 2000 as the predictor for biomarker publication trends, this trajectory analysis gives each biomarker a simple

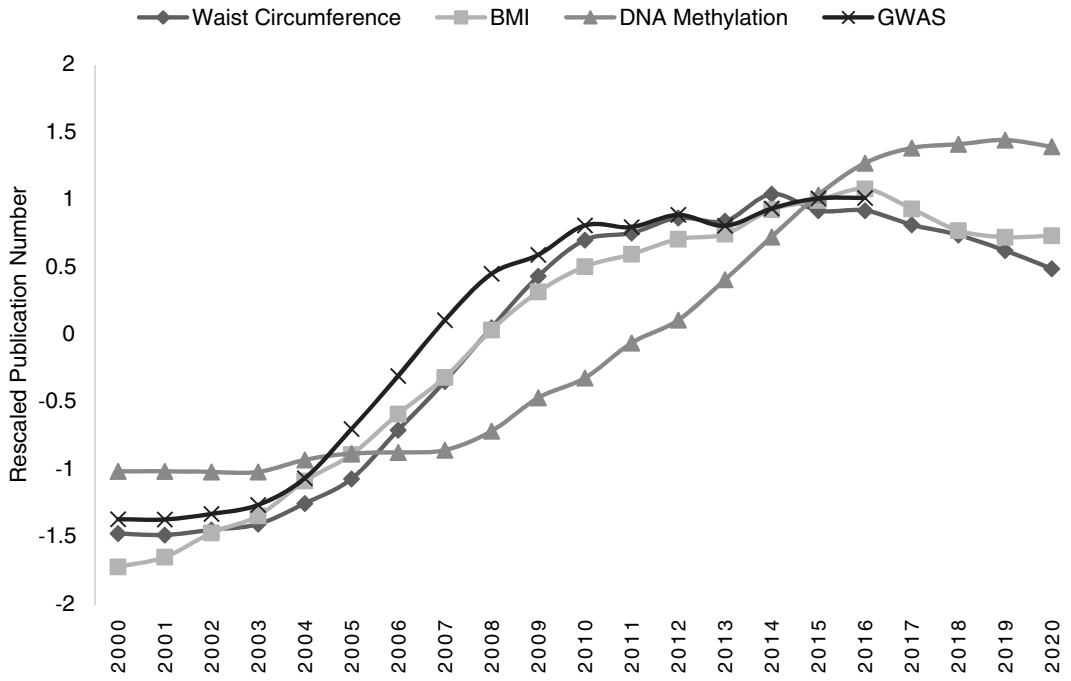

FIGURE 3 Relative growth of four illustrative biomarkers in developmental sciences following the learning curve

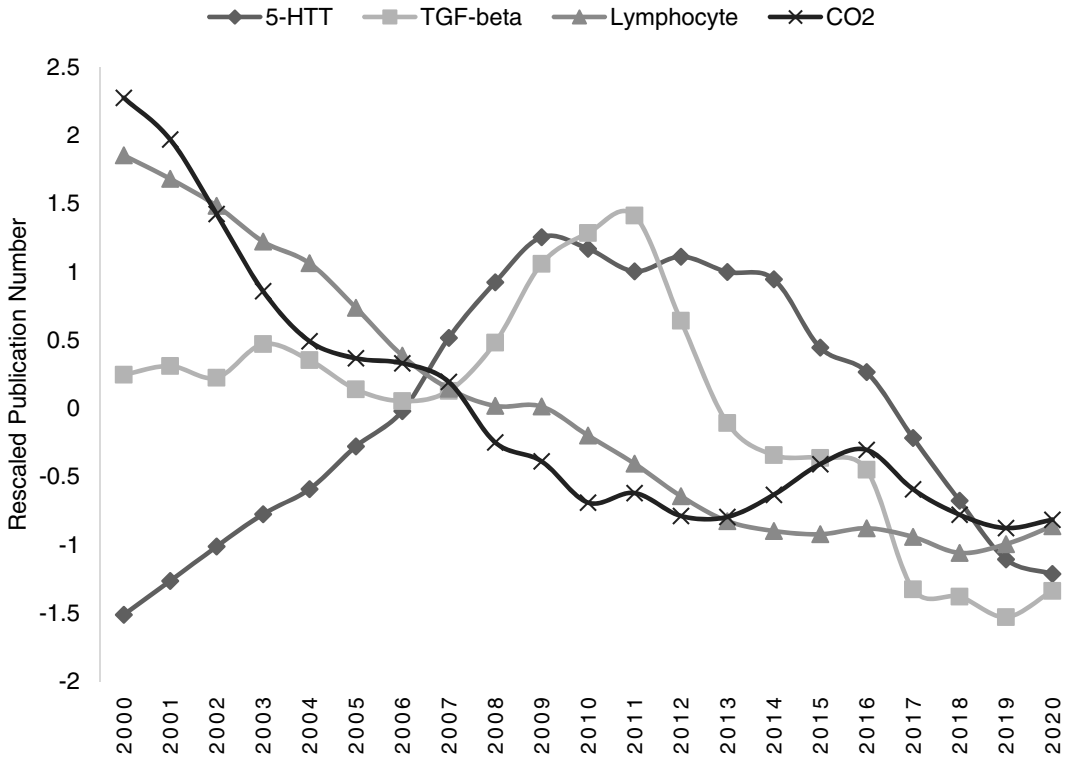

FIGURE 4 Growth of four illustrative biomarkers in developmental sciences not following the learning curve

characterization based on its existing trajectory, including rising, dwindling, and boom–bust trajectories. The existing relative publication trends across years for each biomarker was regressed on the linear, quadratic, and cubic time variables, with the biomarker-specific intercept, linear, quadratic, and cubic coefficients recorded. To make coefficients comparable, we standardized the publication trends across years for each biomarker before regression. Then, we plotted the intercept, the linear, and the quadratic coefficients against the ratio of the higher power coefficient over the coefficient in a series of three scatterplots. By portraying the coefficients against a higher power coefficient that can differ in both direction and magnitude, this series of scatterplots offers insights into the rate of change in publication trends, allowing researchers to see how the trajectory of a new biomarker or other scientific topic would fit the simple characterizations. It should be noted that this descriptive analysis is not meant to offer predictive ability but solely as a high-level description of existing trajectories.

In Figure 5a–c, we depicted the scatterplots between the intercept and the linear-intercept ratio, between the linear term and the quadratic-linear ratio and between the quadratic term and the cubic-quadratic ratio, respectively. We labelled examples of the plateauing learning curves, the boom–bust curves (bold font), and the steady declining curves (italic font) from Figures 2 and 3 to demonstrate the range of coefficients and ratios that appear to capture the different types of trajectories.

From Figure 5, the steady decline trajectories (lymphocyte and CO_2) tend to have large positive intercepts (over 2) and a negative quadratic-linear ratio (around -0.15), a pair indicating a high starting point followed by considerable declines. From Figure 5c, the boom–bust trajectories (5-HTT and TGF-β) have small and positive cubic terms (below 0.002), but a larger and negative quadratic-linear ratio (below -0.5). Beyond these two consistent mappings between types of trajectories and locations on the scatterplot, no signature locations on the three scatterplots appear to capture the learning curve, which can be the result of many combinations of the coefficients and the ratios considered.

3.3 | Biomarker groups

The third part of the descriptive analysis on biomarker content grouping is shown in Figure 6. To better portray the trend of publications for biomarker groups, we again conducted smoothing that accounts for the mean of adjacent points (Jones & Roediger, 1995). Not all 90 biomarkers are included for the grouping analysis and there could be many other grouping constructs, such as tissue type, method of collection, target outcome, potential for intervention, etc. The full list of biomarker groupings for the current paper is documented in Table S4. Given that publication trends differ greatly by biomarker, aggregating all publications from biomarkers within each group would be biassed by the more commonly used biomarkers. To present a less biassed picture, we first standardized the publication trends across years for each biomarker, before taking the mean of the standardized publication trends for each year across all biomarkers within a given group. For this analysis, we clustered 38 measures into 5 groups: aging measures (C-reactive protein [CRP], Cystatin-C, haemoglobin A1c [HbA1c], insulin-like growth factor 1 [IGF-1], interleukin 6 [IL-6], N-terminal pro-brain natriuretic peptide [NT-proBNP], tumour necrosis factor α [TNF-α]), blood count measures (eosinophils, monocytes, neutrophil, platelet volume, red blood cell, total protein, triglycerides, white blood cell), brain-based measures (cortical thickness, resting state magnetic resonance imaging [MRI], structural MRI, total brain volume, task-based functional MRI [fMRI]), common medical (BMI [body mass index], diastolic blood pressure, glucose, LDL [low-density lipoprotein], systolic blood pressure, total cholesterol, waist circumference), and molecular (DNA, DNA methylation, epigenetic clock, genetic, genome-wide association studies [GWAS], ribonucleic acid [RNA], telomere length).

A visual inspection of Figure 6 indicates that most groups follow a roughly similar learning curve trajectory. Aging measures grew in popularity until plateauing in mid 2010s. Blood count measures, the non-learning curve group, appeared to have declined in popularity in the early 2000s before growing in the mid-2010s. Brain-based measures grew steadily throughout our time frame. Common medical measures appear to have peaked in the

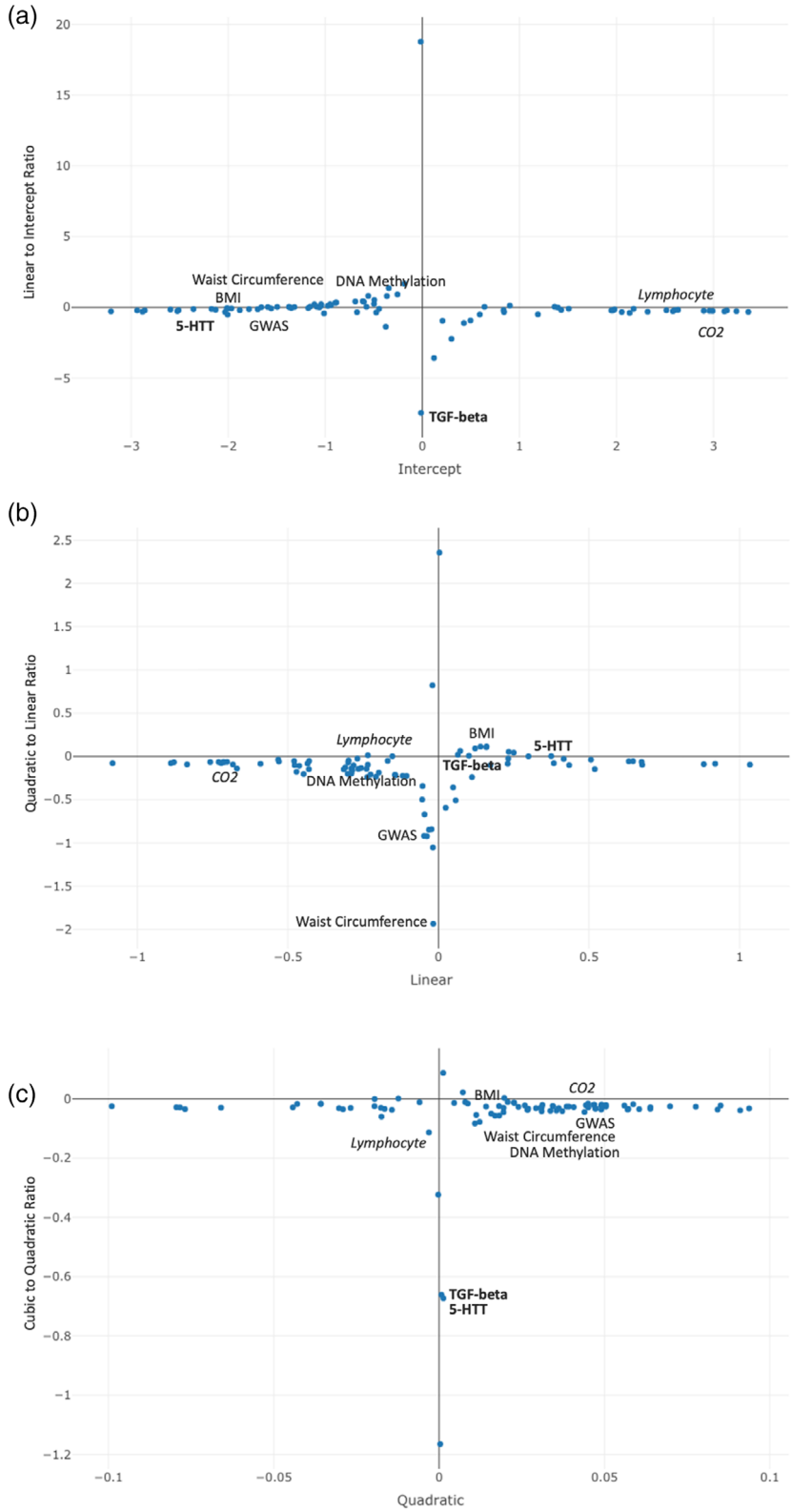

FIGURE 5 (a) Intercept and linear-intercept ratio; (b) Linear and quadratic-linear ratio; (c) Quadratic and cubic-quadratic ratio See Table S3 for data for these figures

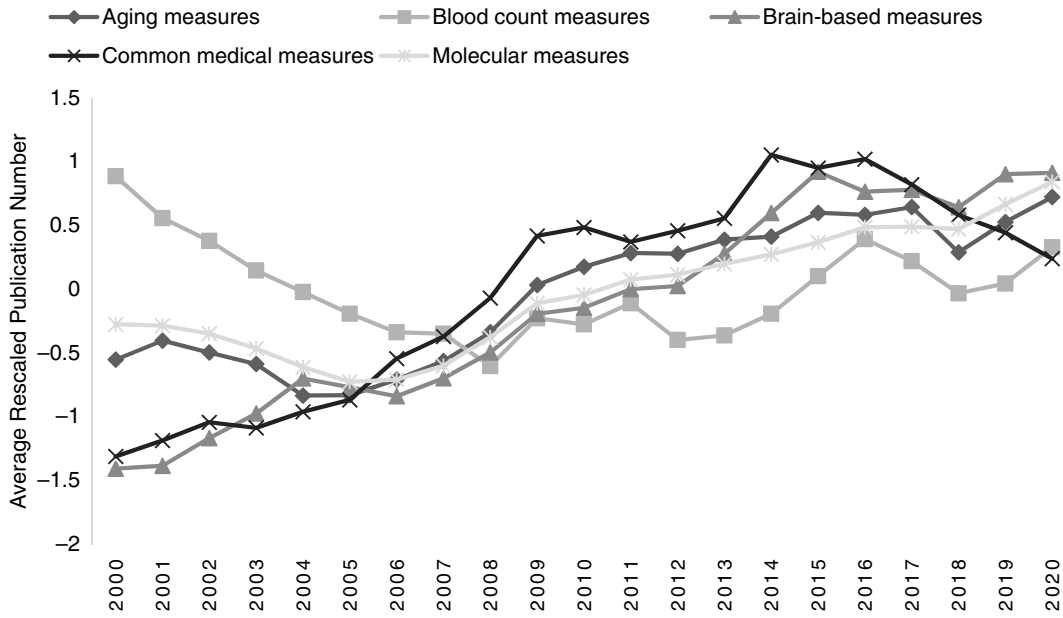

FIGURE 6 Average rescaled biomarker publication trends mean smoothing for content groups

mid-2010s while dipping in popularity afterwards. Finally, the molecular measures grew since mid-2000s, but at a slower rate after the mid-2010s.

3.4 | Modelling trajectory associations

Recall that the second set of analyses focused on examining potential predictors of future biomarker publications using two modelling frameworks (multi-level and random forest). Ultimately this would provide researchers and funders the ability to understand and estimate where a particular biomarker is on its trajectory of adoption.

3.4.1 | Multilevel model

The polynomial multilevel model was fitted with the lme4 package in R (v1.1–26; Bates et al., 2015), with a random slope for the linear effect of year number allowed for different biomarkers. All predictors included were on level-1, the level of yearly publication outcomes. No level-2 predictors were used in our analysis. The polynomial multilevel model was fitted with the whole dataset to obtain parameter estimates and overall model performance in explaining variance with the fixed effect part of the model.

Table 1 contains the parameter estimates and significance information. Besides the intercept, all retained predictors are significant. The forward and the backward selection processes found the same set of variables, including linear, quadratic, and cubic number of years since the first publication, as well as affiliation number (5 years ago) and scaled NIH funded project number (5 years ago). This set of variables selected allows for making predictions 5 years into the future, as the only historical statistics used are from 5 years ago. The linear and cubic year numbers are positively associated with the outcome variable, but the quadratic year number has a negative association. The cubic term, although significant, has practically 0 effect on the publication trends, with the effect becoming perceptible only after 100 of years have passed since the first publication. The coefficient for the year related predictors

TABLE 1 Parameter estimates and significance information

	Estimates	SE	df	*t*-value	*p*
Intercept	−0.0505	0.0308	130	−1.64	.103
Linear year number	0.00495	0.00137	337.5	3.61	<.001
Quadratic year number	−0.00006	0.00002	710.1	−2.67	.008
Cubic year number	0.00000*	0.00000*	633.4	4.02	<.001
Affiliations 5	−0.00009	0.00001	1296	−17.06	<.001
Adjusted NIH project number 5	0.56	0.264	1347	2.12	.034

**Note*. While the cubic year number has statistical significance, it has practically zero effect with minuscule coefficient, thus rounding to 0 with five digits after decimal. Affiliations 5 = affiliation number (5 years ago). Adjusted NIH project number 5 = adjusted NIH funded project number (5 years ago).

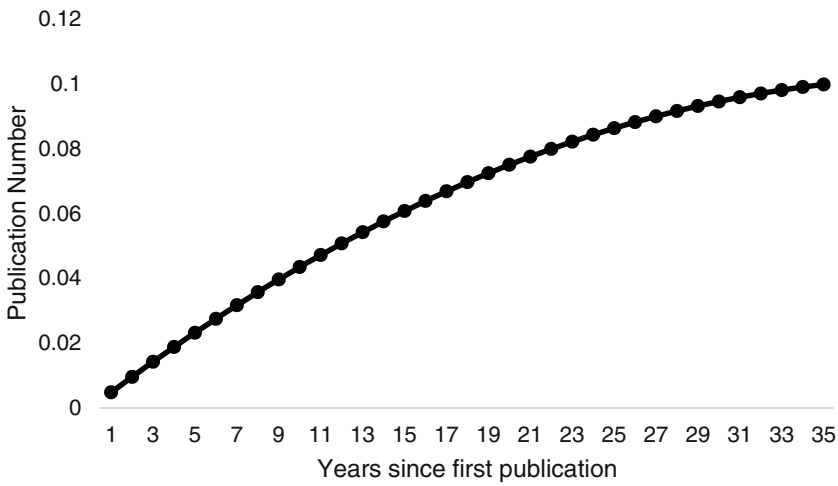

FIGURE 7 Visualizing effect of linear and quadratic terms

means that, taken together, the initial linear increase is gradually overtaken by a decrease from the quadratic effect, as seen in Figure 7, where a curve was plotted to show the effect of the linear and the quadratic terms for a hypothetical biomarker during the first 35 years of publication. The affiliation number has a negative coefficient on publication trends 5 years into the future, whereas the NIH project number has a positive coefficient. Because the effect sizes of multilevel models are a topic that is still being researched, with no definitive approach to compute the effect sizes as would be the case for linear regression, we did not obtain effect sizes for predictors. The model fitted on the full dataset has an R^2 of 0.101 for the fixed effect. Similarly, with the small magnitude of the outcome variable, the assessment of predictive ability relying on root-mean-square deviation (RMSE) was no longer meaningfully interpretable. As a result, we took the absolute difference between the predicted value and the actual value to compute a percentage of prediction deviation with the predicted value as the base. This statistic offered intuitive interpretations and comparability across different models. The predicted value was chosen as the base rather than the actual value because the possible actual value of 0 would return an infinity error. The median percentage deviation for the multilevel model was 9.0%. Because the multilevel model was fitted with all biomarkers as level-2 units, we did not perform cross-validation, which may change the number of level-2 units retained for fitting the multilevel model.

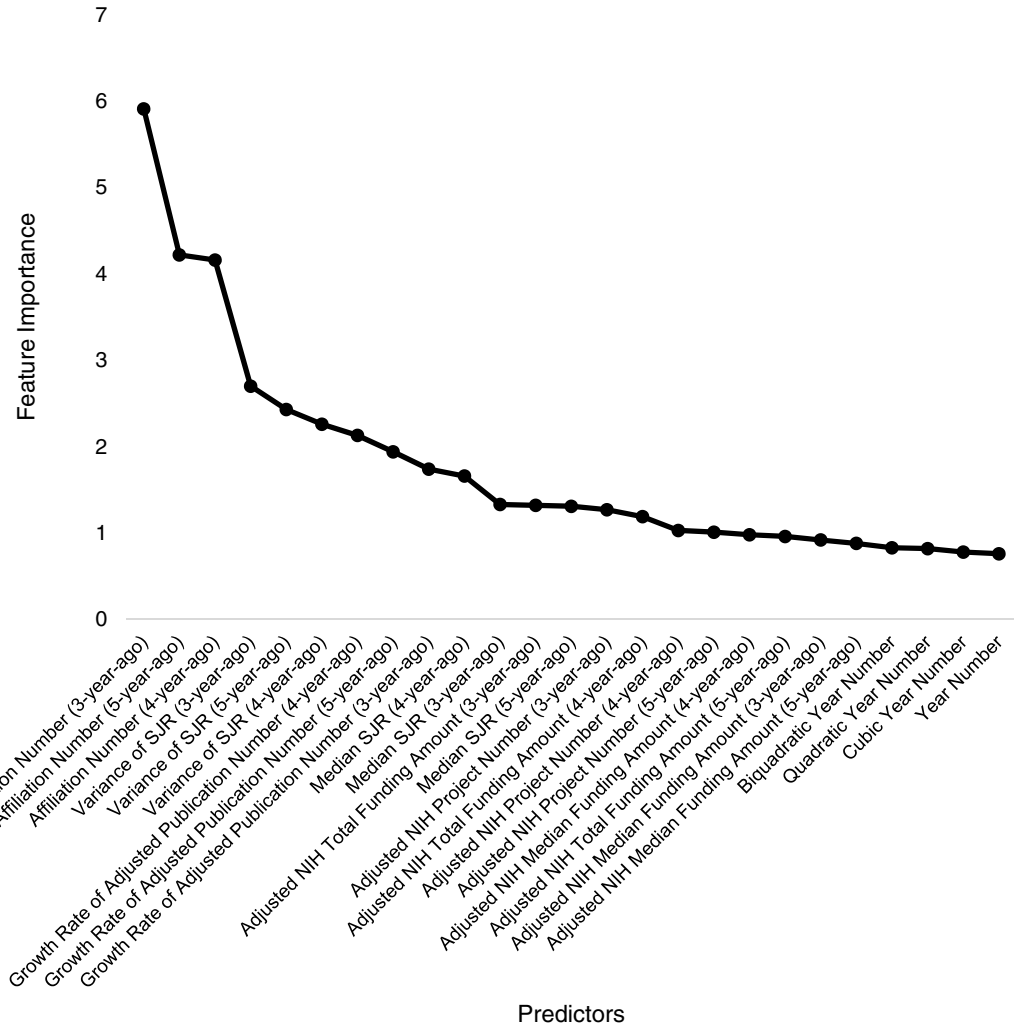

FIGURE 8 Random Forest model feature importance

For the random forest model, we included all the available predictors first. From the overall dataset, we obtained the feature importance for each of the predictors, ranked from the most to the least relative contribution to decreasing the outcome variance at the tree splits where the corresponding predictor was featured. Figure 8 presents the ranked feature importance from the highest to the lowest for all predictors. Based on the plot, it appears that among the predictors included, the number of affiliations from 3 to 5 years ago had the highest feature importance. Following the affiliation numbers, the variance of SJR and growth rate of publication numbers from various years in the past, as well as the median SJR from 4 years ago, had relatively high feature importance. Further predictors along the ladder of importance appeared to have taken a step down compared to the previous predictors. To prevent the overfitting of the model to the data, we conducted a 100-time cross-validation, essentially splitting the dataset randomly without replacement into a 75% training set and a 25% testing set for 100 times. During each split, the random forest model was fitted with the training set, while we recorded the median percentage deviation statistic obtained with the trained model applied to the corresponding testing set. The cross validation median percentage deviation for the random forest model ranged from 6.5% to 7.1%, with a mean of 6.8%, and a median of 6.8%. This model performance metric demonstrates a marked improvement over the performance of the polynomial multilevel model.

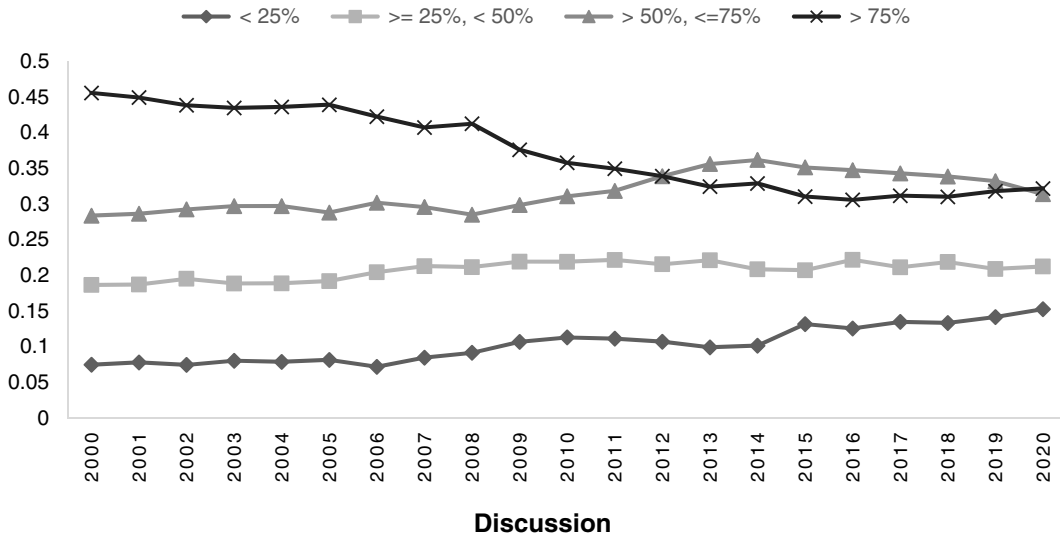

FIGURE 9 Journal impact tier and growth among all biomarker publications

To make future predictions at the biomarker level, we refitted the random forest model with the full dataset in order to make future 3-year predictions for all the included biomarkers. The same set of predictions was conducted with the polynomial multilevel model, albeit allowing the predictions for the next 5 years. The predictions for the popularity of the biomarkers are shown in the interactive plot previously discussed. In this interactive plot, viewers can visualize both the historical publication trend and the future popularity prediction for either single biomarkers or multiple biomarkers comparatively. Viewers can also compare the predictive results from the two modelling frameworks we adopted.

To summarize the future prediction for all 90 biomarkers, we have provided the value and the rank of the projected popularity of the biomarkers in year 2023 in Table S2. We chose to present the year 2023 because it is the furthest year from the end of the data sampling, year 2020, while still allowing for averaging the prediction results from both the polynomial multilevel model and the random forest model. Beyond presenting the ranks of the predicted publication trends, we also computed the change in projected popularity by the two models relative to the 2020 publication trends. The percentage change relative to 2020 popularity and the rank of percentage change were also included in Table S5. Among the 90 biomarkers, 13% have percentage increases larger than 10%, while 69% of the biomarkers have percentage decreases larger than 10%. We define these biomarkers as either projected to increase in popularity or projected to decrease in popularity, whereas for the remaining 18% of biomarkers, we define them as plateauing in terms of publication trends.

3.5 | Trends based on journal impact factor

In a follow-up analysis, we examined the trajectory of biomarkers grouped based on the SJR indicator for all the publication outlets encountered in our publication search. The goal is to document if publications for all the 90 biomarkers are gradually shifting to higher or lower ranking journals, as shown in Figure 9. Because journal outlets ranking shifts across years, to give a consistent definition of what journals are of higher or lower ranking, we divided all existing journals up into four quartiles based on the SJR from 2020 before tabulating the proportion of all biomarker papers queried for each year between 2000 and 2020 that fall into each of the 2020-based journal quartiles. Publications without 2020 SJR ranking for the journal outlet are not included in the figure. For each year, the

proportion of publications in each quartile sums up to 100%. This analysis demonstrates a decrease in biomarker publications appearing among journals within the top quartile (i.e., highest impact factors). At the same time, journals from the lowest ranking quartile and the second-to-top quartile have steadily grown to account for larger proportions of biomarker publications. The second quartile of journals also saw an increase in biomarker papers, albeit a modest one.

4 | DISCUSSION

Using the publicly available information for 90 distinct biomarkers between 2000 and 2020, we sought to document and understand the general trend of biomarker adoption in publications relevant to developmental science, as well as to explore the potential predictors behind their growth. We used a metascience perspective that was content agnostic, allowing us to identify common drivers of biomarker use without regard to the substantive research topic. Most biomarkers followed the "learning curve" model, and though the rate of the growth differed by biomarker, there was a pattern of a rapid initial rate followed by slower, more consistent growth. In addition to documenting changes across time, we developed two models to predict the publication trends for the biomarkers, finding that we were able to make relatively precise predictions for future popularity of the included biomarkers given historic publication and funding data. The two models were constructed from different modelling frameworks to present a diverse set of predictions and is less likely to be vulnerable to specific assumption violations. Both the explanation and the prediction components of the models offer important utilities. The explanations based on the interpretation of the models reveal what factors contributed to the growth in biomarker adoption patterns. The predictions, on the other hand, offer insight into the likely trajectory of any given biomarker.

In general, the patterns of publications most closely resembled a learning curve. The combination of the direction and magnitude of the three significant time-related predictors together resembles a general popularity growth curve that accelerates in the beginning, slows down in the middle, and is followed by a smaller accelerated growth or plateau after the slowdown. The consistency with which this general trend was found is remarkable. However, it is possible that more transitory biomarkers saw so few publications as to never gain a foothold long enough to arrive on our list of biomarkers. Nevertheless, it does appear that developmental researchers incorporate biomarkers into products in a remarkably similar way. In fact, only four biomarkers, *5-HTT* or *SERT*, TGF-β, lymphocyte count, and CO_2 had a publication pattern that did not follow a learning curve model. In the case of *5-HTT*, the majority of the papers under this heading are molecular genetic measures of the length polymorphism of the *5-HTT* gene (Caspi et al., 2003, 2010; Culverhouse et al., 2018; Karg et al., 2011; Munafò et al., 2008; Risch et al., 2009). The literature on candidate genes, and the serotonin-transporter-linked promoter region (*5HTTLPR*) in particular, has been particularly active and contentious over a relatively short period of time (Alexander, 2019). After a very rapid rise, publications on *5-HTT* have seen a rapid decline recently, suggesting a growth more akin to the infatuation cycle or potentially a hype curve (though more time would be needed to determine which pattern it most resembles).

Although most of the 90 biomarkers followed a similar trend in growth over the past 20 years, another key goal of this paper was to explain variations in that growth by using publicly accessible data on publications, funding, and networks from prior years. The purpose was in part to be able to describe some of the driving forces of the growth of these biomarkers. For example, the significant positive effect of the number of NIH projects funded fits expectations that a wide range of supported projects is associated with increases in later publication output. However, the amount of funding was not a significant predictor of the number of projects, suggesting a weaker relationship with future publication trends.

Interestingly, we observed a significant negative effect of affiliation numbers from 5 years ago on publication trends. This is contrary to expectations that topics that have already received widespread interest are in the position to gain even more popularity. Our results indicate that there is an association between a rapid increase in participating research institutes and decreased future biomarker popularity, lending support to the idea that a sudden influx of

interest may precede a deceleration in the growth of research output (potentially an indication of hype—though not following the hype curve). It is possible that as a biomarker becomes accessible for research by more institutions, by definition, it becomes less unique and innovative, lowering its value for publication. Also, as more researchers use the biomarker, it might also be more mature in its lifecycle. Scientists would presumably understand the biomarker's limitations and proper use, thereby reducing the number of publications with misuses of the biomarker. The feature importance metric of the random forest model also demonstrated the importance of affiliation numbers as a driving force behind publication trends. In this model, the affiliation number had the highest contribution in explaining variance in publication trends.

Furthermore, in terms of the random forest model, the feature importance metric also demonstrated that the variance of the SJR index and publication growth rate had the highest contributions to publication trends. Unlike with the multilevel model, with the random forest model, current methods do not allow us to elucidate the direction of relationship between trends and predictors. Thus, while we know that the variance of the SJR index and publication growth rate play an important role in publication trends, we do not know whether a more or less variable SJR index or a lower or higher publication growth rate is associated with increased popularity. Based on our cross-validation process, the random forest model offered a higher prediction accuracy over the multilevel model, thus allowing for more confidence in the use of the prediction result for research activity and funding decision making. The random forest model, which depends on highly nonlinear relation, and the multilevel model, which uses largely linear relations between predictors and the outcome, draw information from distinct sets of predictors. Because the two models rely on distinctive aspects of research to predict future publication trends, users of our work have the freedom to pick the model that best captures their interest. For example, should a specific funding agency be particularly mindful of the variability in the impact factor of journals publishing on a particular biomarker rather than how long the biomarker has appeared in published scientific articles, the random forest predictions should be consulted more than the multilevel model.

Our data driven approach, while allowing us to model the publication trends with publicly available records, has limitations. Publication bias makes it more likely that whether studies translate to publications are based in part on whether the paper includes statistically significant results. Such biases are likely to mask the true use of each biomarker in research. Because we could not correct for publication biases in data, our predictive models could only rely on the assumption that all topics have similar biases in publication activities. Similarly, we acknowledge the limitation in the sources of data we have selected for our analysis. We did not include publication sources beyond the Web of Science, such as SCOPUS or Google Scholar. The overlap of large databases, such as the Web of Science and SCOPUS are high (over 90% for journals), while smaller-more disciplinary specific databases, such as PsycINFO, do not contain nearly as many journals as the Web of Science. Furthermore, the limitation of only searching peer-reviewed journals (i.e., not using Google Scholar) does limit our ability to discuss biomarker work in dissertations, working papers, and presentations. An extension of this work could compare biomarker papers' changes in peer-reviewed and other outlets. Focusing on peer-reviewed articles may have already selected for biomarkers with at least some prior evidence, which may help to explain why so many of the biomarkers have a more sustained "learning curve" style growth. Furthermore, we chose to rely exclusively on NIH for the funding variable, which limited our capability to capture full funding amounts. This decision was similarly motivated by data matching challenges, such that other sources (e.g., the National Science Foundation) provide funding for entire multi-year projects in a single year, disallowing the possibility of aggregating yearly funding. Our use of one impact factor score, SJR, in our secondary analyses to assess the influence of journal reach similar limits the interpretation of our results. There are over 45 different metrics for journal impact, and while some, such as Journal Impact Factor and SJR, are strongly correlated, each metric provides a slightly different measure of journal reach and influence (Glänzel & Moed, 2002; Mech et al., 2020; Saha, 2003). We used SJR because it was both a prominent method of assessing impact and easily merged with our 430,000 articles. Other metrics could prove useful in future analyses. Finally, it should be noted that although there is often a tendency to equate impact factor or ranking with quality, there are strong arguments for why this is not always true, and regardless, it may not be true of the quality of any given article.

In addition, our selected search terms limit the current study to focus only on the first two decades of life, despite substantial development occurring throughout the lifespan. Future research could examine these trends, inclusive of research focused on the years beyond adolescence. Furthermore, our search approach does assume researchers with studies included used a developmental science lens in their research. Given the substantial number of articles (over 430,000) returned by our search, it was not within the scope of this study to screen each article to make this determination regarding the theoretical framing of each study.

Another limitation for our modelling approach involves the nature of our chosen predictors, which are characterized by high collinearity. Although we have taken care with the multilevel model to retain only a few key variables with a model comparison approach, it was nevertheless an incomplete approach that could result in violations of assumptions in the multilevel model. On the other hand, the random forest models should not be affected by the correlated predictors with the random selection of predictors at decision points. Taken together, future efforts should seek to address these weak points in both the source of data and the modelling approach.

Researchers who study infants, children, and adolescents have increasingly answered calls to be interdisciplinary (Duncan, 1991; Michel & Moore, 1995) and examine functioning across multiple levels (Falk et al., 2013; Insel, 2014; Pollak, 2015). Such approaches have already yielded important new knowledge related to normative development, the effects of adversity, and predictors of long-term life outcomes (e.g., morbidity and mortality). Potential lessons for developmental scientists working in this area are perhaps less prescriptive (i.e., what biomarkers are more or less promising to guide future research; though the shape of the curves may sway researchers to avoid those biomarkers following a "hype" rather than a "learning" curve pattern), but instead fall into a category of meta-science recommendations. There are important considerations regarding biomarker adoption, particularly when team members have insufficient training, especially in the context of small, cross-sectional samples, and unspecified theoretical models. We hope to encourage best practices within the developmental science community through the explicit encouragement of collaboration with those who have expertise and training in the biomarkers of interest, pre-registration (to indicate the degree to which biomarker selection was informed by theory), and data sharing (including sharing code/data to allow for replication and for smaller datasets to be combined to create larger samples; in concert with the Open Science Framework (Foster & Deardorff, 2017; Open Science Collaboration, 2015), which allows for researchers to garner precise estimates. In addition, collaborations with methods experts who can bring experience to collection, storage, assaying, and interpretation. Sharing these procedures, analytic approaches, and results transparently is consistent with open science practices, and may usefully accelerate the utility of biomarkers (including when to "invest" or "disinvest" based on their demonstrated performance). More broadly, research networks focused on improving the use of specific popular biomarkers, such as the Telomere Research Network and genetic and epigenetic consortia, bring together stakeholders to develop and disseminate best practices for biomarker measurement. Taken together, our findings indicate that integration of biological and research on human development is likely to continue to grow, and the primary patterns of integration appear to follow a classic learning curve of adoption in the past 20 years, suggesting a period of rapid growth in interest followed by a plateau in the literature. Assuming a positive trajectory or even a plateau following initial growth implies utility of the biomarker in the field, a more consistent growth like the learning curve suggests that a given biomarker may be important for the field.

AUTHOR CONTRIBUTIONS

Weiqiang Qian: Formal analysis; methodology; software; writing – original draft. **Chao Zhang:** Data curation; formal analysis; investigation; methodology; software; visualization; writing – original draft. **Hannah Piersiak:** Methodology; project administration; writing – review and editing. **Kathryn Humphreys:** Conceptualization; funding acquisition; project administration; supervision; writing – review and editing. **Colter Mitchell:** Conceptualization; funding acquisition; methodology; project administration; supervision; writing – original draft.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/icd.2366.

DATA AVAILABILITY STATEMENT

In addition to providing a dataset of the 90 biomarkers for each of the 20 years (https://osf.io/ksj2n/?view_only=5eea3aeaf3b541dba289f226c026c63e), DOI 10.17605/OSF.IO/KSJ2N, we created a visualization tool for charting the trends within developmental science research (https://hypecurve.shinyapps.io/hypecurve/).

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SUPPORTING INFORMATION

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

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