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Regular Article

Differential susceptibility 2.0: Are the same children affected by different experiences and exposures?

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Abstract

Differential susceptibility theory stipulates that some children are more susceptible than others to both supportive and adverse developmental experiences/exposures. What remains unclear is whether the *same* individuals are most affected by *different* exposures (i.e., domain general vs. specific). We address this issue empirically for the first time using, for illustrative and proof-of-principle purposes, a *novel influence-statistics' method* with data from the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care. Results indicated that previously documented effects of greater quality of care on enhanced pre-academic skills and greater quantity of care on more behavior problems apply mostly to different children. Analyses validating the new method indicated, as predicted, that (a) the quantity-of-care effect applied principally to children from more socioeconomically advantaged families and that (b) being highly susceptible to both, one or neither childcare effect varied as a function of a three-gene, polygenic-plasticity score (serotonin transporter linked polymorphic region [*5-HTTLPR*], dopamine receptor D4 *[DRD4]*, brain-derived neurotrophic factor [*BDNF*]) in a dose–response manner (i.e., 2>1>0). While domain-specific findings involving child-care effects cannot be generalized to other environmental influences, the influence-statistics' approach appears well suited for investigating the generality–specificity of environment effects, that is, of "differential, differential susceptibility."

Keywords: differential susceptibility, childcare, domain specific, domain general, polygenic

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Differential susceptibility theory stipulates that some individuals are more susceptible than others to the positive and the negative effects of, respectively, supportive and adverse developmental experiences (e.g., harsh parenting) and environmental exposures (e.g., dangerous neighborhood) (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). Empirical support for differential susceptibility thinking comes from both observational studies of Gene × Environment interaction (G×E) (for review, see Belsky & Pluess, 2009, 2013; Ellis et al., 2011), as well as from experimental research using measured genes as moderators of intervention efficacy (for review, see Belsky & van IJzendoorn, 2017).

What has never been clear – yet repeatedly noted – in all the just cited work is whether such differential susceptibility to environmental influence is domain general and thus trait like or domain specific. That is, are the *same* children affected more than others by *different* experiences and exposures? For example, are children who appear disproportionately affected by the quality of parenting the same ones who prove most susceptible to peer influence? Relatedly, are the children whose problem behavior is most affected by the harshness of parenting the same ones whose language development is most influenced by the richness of their home language environment? In other words, how specific is susceptibility with respect to both developmental "inputs" (e.g., day care, parenting) and/or "outputs" (e.g., aggression, cognition). Are children, then, "differentially, differentially susceptible"?

To many it might seem unlikely that there could be a more or less general trait of environmental susceptibility/developmental plasticity given it is likely that different developmental experiences and environmental exposures probably affect different neurobiological processes and, thereby, distinct phenotypes. From that perspective, why would it be expected that susceptibility to the effects of harsh parenting would have anything to do with susceptibility to the effects of language stimulation; or even why would susceptibility to peer pressure have anything to do with susceptibility to parental discipline? However reasonable such questioning would seem to be, much of the writing about differential susceptibility has seemed to imply, if not explicitly postulate, a more general trait of susceptibility to environmental influences.

Consider first the theory of biological sensitivity to context by Boyce and Ellis (2005), which characterizes some children who are highly susceptible as "orchids" and others who are not as "dandelions." Consider next Aron and Aron's (1997) notion of the "sensitive person," which explicitly calls attention to general variation in sensitivity to environmental influences. In truth, the issue of domain-general versus domain-specific susceptibility

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has really only been mentioned in passing in almost all discussion of differential susceptibility, including by an author of this paper, rather than being given the theoretical and empirical attention it clearly merits. This may well be the result of Belsky, Bakermans-Kranenburg, and van Ijzendoorn's (2007) widely disseminated figure depicting one group of individuals that is highly susceptible and another that is not susceptible at all. Finally, many studies of differential susceptibility (reviewed in Belsky & Pluess, 2009, 2013; Ellis et al., 2011), whether focused on temperament, physiology or genes as moderators of environmental effects, have repeatedly shown that the same putative plasticity factors moderate – in very similar ways – the effects of a wide variety of environmental factors (e.g., prenatal stress, maternal empathy, marital conflict, teacher–child conflict, economic hardship) on a wide variety of developmental phenotypes (e.g., externalizing problems, executive function, attentional bias, sleep, pubertal development). In other words, however simplistic a general trait-like view of susceptibility to environmental influences might appear, this possibility would seem to be widely entertained if not embraced.

Here we address these issues for the first time, drawing – for illustrative and thus proof-of-principle purposes – on data from the large-scale and well-known National Institute of Child Health and Human Development (NICHD) study of early childcare and youth development (Early Child Care Research Network (ECCRN), 2001; 2005). We reconsider two previously documented and widely discussed effects of childcare on children's development prior to school entry at age 4.5 years. These indicate that (a) better *quality* of care predicts enhanced *cognitive* functioning (i.e., better pre-academic skills), whereas (b) greater *quantity* of care forecasts poorer *socioemotional* development (i.e., more behavior problems). We do so in order to determine whether different children are affected by these two distinct exposures and with respect to these two distinct domains of development. If that turns out to be the case (i.e., domain specificity), we test two predictions regarding which children are affected by these distinct experiences. One set of predictions focuses on family socioeconomic conditions and the other on the genetic make-up of the children themselves. Perhaps most worthy of note, we address the issue of domain specificity/generality using a novel approach based on *influence statistics*. To the extent that empirical support emerges for the hypotheses to be advanced, it would suggest that this new approach to investigating "differential, differential susceptibility" is valid and could serve as a valuable tool for investigating this important issue.

What we seek to make clear and explicit, then, is that we regard this effort as illustrative of how further work on domain-general versus domain-specific environmental susceptibility might proceed. We have selected two childcare effects simply because they appear so distinct and widely discussed and emerge from the largest and most comprehensive study of childcare effects to date. Make no mistake, however; this is less a report on effects of childcare than it is an effort to explore a new, influence-statistic approach to investigating differential susceptibility to environmental influences. To the extent that the approach appears informative, it could hold promise for systematically investigating domain-general versus domain-specific susceptibility to environmental influences. We trust that the reader will keep this core purpose in mind.

Effects of Early Childcare

At least three general findings emerged from the NICHD study when effects of childcare, net of a large number of covariates (e.g., family income, parenting, maternal depression), were evaluated as children developed. This included when they were 2 and 3 years of age (NICHD ECCRN, 1998), 4.5 years (NICHD ECCRN, 2002), in kindergarten (NICHD ECCRN, 2003), across the middle childhood years (Belsky et al., 2007) and at age 15 (Vandell, et al., 2010). It is therefore these consistent findings that inform this inquiry. First, as long assumed and well documented, *better quality care* – care that was more attentive, responsive, and stimulating – predicted enhanced cognitive-linguistic development (but not problem behavior). Second, *greater quantity* (or dosage) of care – operationalized as hours per week across months and years – predicted more problem behavior (but not cognitive-linguistic development). Third and finally, both sets of effect sizes were small. Thus, the first new question we address empirically using influence statistics is whether the children who emerge as most susceptible to one of these effects also emerge as most susceptible to the other effect. We advanced no specific hypothesis on this matter. It was, fundamentally, an empirical question.

The Role of Family Socioeconomic Conditions

What was never considered in the multiple evaluations of childcare effects in the NICHD study, as our first focus implies, was whether those children whose cognitive-academic development was (somewhat) enhanced by exposure to higher quality care were the same children who were (somewhat) prone to develop behavior problems as a result of lots of time spent in nonparental childcare across their opening years of life. This seems a notable omission in light of evidence that it is often socioeconomically disadvantaged children who benefit cognitively the most from early intervention or high-quality preschool programs (e.g., Dearing, McCartney, & Taylor, 2009; Duncan & Magnuson, 2013; Schmerse, 2020; Votruba-Drzal, Coley, & Chase-Lansdale, 2004). The general interpretation of such findings is that children from socioeconomically disadvantaged families secure greater developmental support when reared outside the home; and this is often because high-quality care "compensates" for the limited psychological and economic resources of the children's families. The latter are themselves presumed to be due to poverty, racism, and other contextual stressors, including parents' own developmental histories of growing up in socioeconomically disadvantaged households.

Consistent also with the possibility that different children are affected by different features of childcare is the contrasting view that children from more socioeconomically advantaged families secure perhaps less contextual support and lower caregiver investment when care is provided by non-family members than would be the case if they were reared at home by their parents (NICHD ECCRN, 2006). This could thus promote the development of behavior problems.

Should evidence emerge when addressing the first question posed above that different children account for the quality-of-care effect and the quantity-of-care effect under consideration, in line with what has been labeled the "compensatory/lost-resources" hypothesis just articulated (NICHD ECCRN, 2006), we predicted that the two sets of children would come from different households: those most affected by quality of care would come from less socioeconomically advantaged families, whereas those most affected by quantity of care would come from more socioeconomically advantaged families.

The Role of Child Genetic Make-up

Given repeated evidence in both observational and experimental-intervention research that children's genetic make-up distinguishes

those who prove more and less susceptible to environmental effects in a differential-susceptibility-related, "for-better-and-for-worse" manner (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007), our second hypothesis focuses on such personal characteristics. Drawing on three polymorphisms selected a priori based on prior differential-susceptibility-related findings (for review, see Belsky & Pluess, 2009, 2013; Belsky & van IJzendoorn, 2017) and their availability in the NICHD study data set, we predicted that children who prove especially susceptible to the effects of *both* childcare quality and quantity would score highest on a polygenic plasticity score reflecting number of presumed "plasticity alleles." We further predicted that those evincing the least susceptibility to *both* features of childcare would score lowest and that those proving most susceptible to *just one* of these childcare features would score in between these other two groups. In other words, there would be a dose–response relation linking number of plasticity alleles and heightened susceptibility to childcare effects.

Many critiques have been made of genetic research that focuses, as we do herein, on one or a few genetic variants in behavioral research (Manuck & McCaffery, 2014; Moffitt & Caspi, 2014; Moffitt, Caspi, & Rutter, 2005, 2006; Salvatore & Dick, 2015). Concerns have been raised about statistical power, multiple testing, and, perhaps most importantly, hard-earned appreciation that most phenotypes are influenced – or at least predicted by – numerous genes. This is because individual genes have proven to have strikingly small effects, with rare exceptions. In focusing on three select genes in the current inquiry, we do not reject these critiques; to the extent possible, they inform our decision making.

Most worthy of note, as we are limited in the available data set to only a limited number of polymorphisms, we focus on three that we have previously identified as the ones that have most consistently proven to moderate environmental effects in a differential-susceptible-related manner in prior (published) G×E research, that is, our best bets (Belsky et al., 2015, Table 2). These are serotonin transporter linked polymorphic region (*5-HTTLPR*), dopamine receptor D4 (*DRD4*) and brain-derived neurotrophic factor (*BDNF*). Whereas initial, candidate G×E research based gene selection on the "biological plausibility" of how a gene might influence a phenotype, we eschewed that basis of gene selection – just as genome-wide association studies (GWAS) based, "theory-free" work has. As Zhang and Belsky (2020) make clear, the biological-plausibility arguments that figured importantly in candidate G×E work were implicitly if not explicitly based on a diathesis-stress model of Person × Environment interaction and most certainly not on a differential-susceptibility one. This is because gene selection in psychiatric research was based on pre-existing associations between the candidate gene in question and either the phenotype to be predicted or some correlate of the phenotype, like a neurotransmitter (e.g., Caspi et al., 2002, 2003). Thus, virtually all psychiatric-genetic research was based on dual-risk thinking: problems emerge when an environmental risk and a genetic risk co-occur.

In contrast, differential susceptibility research is based on the notion that there may exist genes not so much for psychiatric phenotypes that serve as "vulnerability genes" (Rutter, 2006), but for developmental plasticity and therefore they function as "plasticity genes" (Belsky et al., 2009). Thus, to repeat, it was not biological plausibility claims that led to our gene selection, but simply our reading of the empirical evidence. Finally, out of concern for multiple testing and thus multiple comparisons, we designed our study to test a simple linear trend with respect to cumulative genetic plasticity, as herein operationalized, and its association with susceptibility to both, one or neither childcare effect being investigated.

Identifying Susceptible Children

To date, all differential-susceptibility-related G×E research has involved exploratory tests of Person × Environment interaction. In this body of work a presumed genetic plasticity factor, defined either in terms of a candidate gene or polygenic score, is used to determine whether it moderates the effect of an environmental factor on some psychological or behavioral "outcome." Once an interaction proves significant, it is decomposed to determine if its form is consistent with a hypothesized model of Person × Environment interaction (e.g., diathesis stress); and this is required because it cannot be presumed that the interaction detected in exploratory testing arose for the reasons hypothesized. Here we adopt a different approach, based on influence statistics, to identify children who are more and less affected by each of the childcare exposures being investigated – before considering factors that might account for variation in susceptibility to quantity and quality of care effects (i.e., family socioeconomic conditions, polygenic score).

Influence statistics illuminate which individuals in a sample are more and less responsible for the estimate of any detected association of interest (e.g., Belsley, Kuh, & Welsch, 1980; Cook & Weisberg, 1982). This is accomplished by a "leave-one-out" approach, that is, re-running the association in question repeatedly, each time dropping a single case, to see whether such (minor) sample modifications result in the association increasing (i.e., a negative influencer) or decreasing (i.e., a positive influencer), usually ever so modestly. Such influence statistics have typically been used to identify outliers who are subsequently dropped from the sample because of their disproportionate – and presumed distortive – effect on the association under investigation. Here we use a variation on this more common approach by scoring each and every case in terms of the *degree and direction* of its influence on the associations that are the focus of this report (i.e., effects of quality and quantity of care on, respectively, preacademic skills and behavior problems). Those cases that, when dropped, result in an association decreasing are given positive values reflecting the degree of their apparent susceptibility to the childcare feature in question; in contrast, those cases which, when dropped, result in the same association increasing are given negative values reflecting the degree of their apparent insensitivity to the influence of the childcare feature.

Current Study

Herein we treat these directional influence statistics to address three issues. The first is whether children who prove more and less susceptible to the effects of quality of care on preacademic skills differ from those who prove more and less susceptible to the effects of quantity of care on problem behavior. We do this in two ways, treating degree of influence as both a continuous parameter and categorically (i.e., terciles). If different children emerge as responsible for these quality and quantity effects, we test the two aforementioned hypotheses regarding family socioeconomic characteristics and child genetic make-up (i.e., second and third issues). Recall that the ultimate goal of this work is less to determine whether two different features of childcare principally affect the same or different children than it is to investigate

the utility of the influence-statistic approach. To the extent that hypotheses receive empirical support, it would suggest that this novel method could prove useful in addressing the general issue of domain generality/specificity in the case of environmental effects.

Method

Participants

Families were recruited through hospital visits to mothers shortly after the birth of a child in 1991 in 10 locations in the United States. During selected 24-hr intervals, all women giving birth ($n = 8{,}986$) were screened for eligibility. From that group, 1,364 families completed a home interview when the infant was 1 month old and became the study participants. Details of the sampling plan can be found in NICHD ECCRN (2005). In terms of demographic characteristics at study enrollment, 26% of the mothers had no more than a high school education and 21% had incomes no greater than 200% of the poverty level.

Overview of data collection

The current inquiry builds directly on an earlier report examining effects of quantity and quality of childcare just prior to children's entry to school, at 54 months of age, which revealed differential effects that we re-examine herein of childcare quality and quantity on, respectively, tested preacademic skills and caregiver-reported problem behavior (NICHD ECCRN, 2002). Children were followed from birth to 4.5 years of age. Mothers were interviewed in person when infants were 1 month old. Detailed measures of home and family environments were obtained by means of interviews and observations when children were 6, 15, 24, 36, and 54 months old. Primary childcare settings were observed at the same ages for all children who were in nonmaternal care on a regular basis for 10 hr or more per week. Mothers were telephoned regularly to update reports on childcare usage. Children's development was assessed at 4.5 years.

Owing to the presence of missing values, we would be missing 600 and 371 children when predicting preacademic skills and problem behavior, respectively, using complete-case analysis. Therefore, we conducted multiple imputation on all variables included in the analysis with the exception of polygenic scores. This yielded a sample size of 1,364, matching the originally enrolled sample, to address the first two issues to be considered – whether the same children are more or less susceptible to different features of childcare and whether evidence of domain-specific susceptibility, should it emerge, is associated with family socioeconomic status. When investigating the association between the polygenic score and the influence-statistics' index of susceptibility, we restricted analysis to only the white subsample that provided DNA ($N = 449$).

Measures

We first delineate childcare predictors, followed by dependent child outcomes, followed by covariates, followed by genotyping.

Childcare predictors

Quantity

During telephone interviews conducted at 3-month intervals through 36 months and at 4-month intervals thereafter, mothers reported hours of nonmaternal care per week that children experienced. The hours spent in all settings for each of the 16 measurement epochs were averaged across ages to reflect mean hours per week from 1 to 54 months of age.

Quality

Observational assessments were conducted in the primary childcare arrangement at ages 6, 15, 24, 36, and 54 months. Quality was assessed during two half-day visits scheduled within a 2-week interval at 6–36 months and one half-day visit at 54 months. At 6, 15, and 24 months, a positive caregiving composite score was created, reflecting the mean of five 4-point qualitative ratings made by highly trained observers (*sensitivity to child's nondistress signals, stimulation of cognitive development, positive regard for child, emotional detachment* [reflected], and *flatness of affect* [reflected]). Cronbach alphas for the composite exceeded .85 at each of these times of measurement. At 36 months, these five ratings and two additional ones (*fosters child's exploration*, *intrusiveness* [reflected]) were included in the positive caregiving composite (Cronbach $\alpha = .83$). At 54 months this composite quality-of-care score was the mean of 4-point ratings of caregivers' *sensitivity–responsivity, stimulation of cognitive development, intrusiveness* (reflected), and *detachment* (reflected) (Cronbach $\alpha = .72$). As in the prior report (NICHD ECCRN, 2002), positive caregiving composites for each age were standardized and averaged across age to create the index of quality of childcare.

Child outcomes

Behavior problems

Caregivers completed the 100-item caregiver-teacher report form developed for children ages 2–5 years of the child behavior checklist (Achenbach, 1991). For purposes of this report, we used the total-problems' score, which is based on the internalizing problems' (Cronbach $\alpha = .90$) and externalizing problems' subscales (Cronbach $\alpha = .95$). Raw scores were converted into standard *T* scores, based on normative data for children of the same age.

Preacademic skills

This measure represents the standardized average of two subtests of the Woodcock–Johnson Achievement and Cognitive Batteries (1990). The letter–word identification test measures skills at identifying letters and words (Cronbach $\alpha = .86$). The applied problems test measures skill in analyzing and solving practical problems in mathematics (Cronbach $\alpha = .85$).

Maternal, child, and family covariates

Measures of maternal, child, and family characteristics were collected and used as controls for selection effects. A *family income-to-needs* (ITN) ratio was calculated from data gathered at 6, 15, 24, 36, and 54 months. The ITN was created by dividing total family income by the poverty threshold for family size. A mean ITN was calculated based on data from 6 through 54 months (see NICHD ECCRN, 2002). *Mother's level of education* (in years), the study children's *race/ethnicity* and *sex*, and the *study site* were collected only at the 1-month interview. The *presence of a husband/partner in the home* was reported in the aforementioned telephone interviews as proportion of measurement epochs through 54 months in which mother reported a husband/partner present. *Maternal depression* was assessed at 6, 15, 24, 36, and 54 months, using the Center for Epidemiological

Studies Depression Scale (Radloff, 1977) (Cronbach α exceeded .85 at each age), a self-report measure of depressive symptomatology; scores were averaged over time.

A composite measure of *parenting* was based on maternal sensitivity ratings and scores of the Home Observation for Measurement of the Environment (HOME) (Caldwell & Bradley, 1984). To assess maternal sensitivity, Mother × Child interactions were videotaped in semistructured, 15-min sessions at 6, 15, 24, 36, and 54 months. Composite sensitivity scores were created from sums of different ratings scales (e.g., maternal sensitivity to child nondistress, intrusiveness, positive regard) (Cronbach α exceeded .70 at every age). The HOME was administered during home visits at 6, 15, 36, and 54 months. Information used to score the items (e.g., parental responsivity, parental involvement, variety in experience) is based on observation and semistructured interview (Cronbach α exceeded .77 at each age). The HOME and maternal sensitivity scores were standardized and averaged within and then across age to create a parenting quality composite score.

Genotyping

DNA was successfully collected from 695 participants in the NICHD study when children were 15 years of age. DNA extraction and genotyping was performed at the Genome Core Facility in the Huck Institutes for Life Sciences at Penn State University. For this report, we selected, a priori, three genetic markers (out of the 59 single nucleotide polymorphisms and four variable number tandem repeats [VNTRs] available) that have been widely used in differential-susceptibility-related research (for reviews, see Belsky & Pluess, 2009; 2013; Belsky et al., 2019). Polygenic plasticity scores were based on the number of putative "plasticity alleles" that each child carried (i.e., 0, 1, 2): s alleles for *5-HTTLPR*, met alleles for *BDNF* and 7-repeats for *DRD4*. This resulted in polygenic scores ranging from 0 to 6. The number of children with 0, 1, and 2 "plasticity alleles" for *5-HTTLPR* is, respectively, 203, 327, and 147; for *BDNF* is 357, 167, and 34; and for *DRD4* 498, 142, and 26. Frequency distributions for *BDNF* (rs6265 $\chi^2 = 5.33$, $p < .05$) departed significantly from Hardy–Weinberg equilibrium (HWE), as did the VNTR *DRD4* ($p < .01$), using exact tests estimated using Markov chains (GENEPOP 4.2; Raymond & Rousset, 1995), but not that of *5-HTT*.

To empirically evaluate potential genotyping errors, we conducted reliability analyses for both the single nucleotide polymorphisms and the VNTRs. Specifically, reliability was ascertained by twice genotyping somewhat more than 10% of the subsample providing DNA; all discrepancies were resolved via a third genotyping. For *BDNF,* 13.4% of available samples could not be genotyped but the others yielded 97% agreement. For DRD4 VNTR, 4.7% of available samples could not be genotyped but the others yielded 83% agreement. For *5-HTT* VNTR, 3.2% of available samples could not be genotyped but the others yielded 80% agreement. As explained in great detail in a prior publication, analysis of potential genotyping errors – via repeated assays – suggested that "deviation from HWE is likely not a strong indicator of genotyping error in the present data" (Belsky et al., 2015, p. 374).

Statistical Analysis

We treated the data as missing at random and conducted multiple imputation on all variables included in this report except for the genetic scores, using multivariate imputation by chained equations (MICE; van Buuren & Groothuis-Oudshoorn, 2011) in R. This procedure generated 20 imputed data sets. All reported results, including the influence statistics, are based on pooled results across these 20 data sets (with the exception of non-imputed polygenic scores).

Before conducting influence-statistic analyses, we first established that, as in the original 4.5-year-old report (NICHD ECCRN), quality of care positively and significantly predicted preacademic skills, but not behavior problems, and that the reverse was true of quantity of care (see Table S1in the supplementary materials). That this proved to be the case with all covariates and both childcare parameters in the prediction model led us to implement the following analyses.

In order to evaluate and distinguish domain specificity/generality of the childcare effects under investigation, we relied on the influence statistic DFBETAS (Belsley et al., 1980). This index quantifies the effect of each single observation on each regression parameter. For example, with two predictors, there could be three DFBETAS for each observation (i.e., participant), indicating the nature and degree of change of each parameter (i.e., one intercept and two slope coefficients, one for each predictor) in standardized units upon removing this single observation. Thus, DFBETAS represent a directional quantity reflecting the direction of influence of a specific predictor of each case, with its absolute value indicating the magnitude of influence.

Given our interests in the influence of each child on the association between specific predictors and outcomes, we focus on the DFBETAS of regression slope coefficients (involving prediction of academic skills using quality of care and problem behavior using quantity of care). For example, a negative DFBETAS' value of −0.1 means that a particular regression slope coefficient decreases 0.1 standard error units when that particular child is included as compared to when she is omitted from the prediction model. In contrast, a positive value of DFBETAS of 0.3 indicates that the regression slope coefficient in question increases 0.3 standard error units when the particular child is included as compared to when he is omitted. Because the associations between childcare quantity and problem behavior and between childcare quality and preacademic performance are both positive, individuals with a positive DFBETAS contribute more to the positive association than those with a negative DFBETAS. In this way, DFBETAS becomes an (apparent) index of susceptibility to the effect of the childcare condition in question, with larger positive values representing greater susceptibility.

Using DFBETAS, we assessed the susceptibility of each child to the effect of quantity and quality of childcare on, respectively, preacademic skills and problem behavior. Procedurally, this involved running separate regressions, one for each outcome, with both quality and quantity of care as predictors, as well as all the covariates previously listed, along with the calculation of DFBETAS for the childcare effects in question.

Using the resultant DFBETAS' measurements, we proceeded to investigate domain specificity and generality – in two ways. One involved continuous DFBETAS' scores and the other categorical scores. Thus, we first correlated the two continuous DFBETAS' scores and then cross-classified their terciled measurements, to determine whether children appearing highly susceptible to the effect of quality on preacademic skills proved highly susceptible to the effect of quantity on behavior problems. Highly positive associations would indicate that the same children proved more or less susceptible to both of these effects.

Table 1. Cross-tabulation of number of children classified as highly susceptible and highly unsusceptible to effects of quantity and quality of care on, respectively, behavior problems and preacademic achievement[a]

	Quantity: Behavior problems		
Quality: Preacademic skills	Susceptibility	Low	High
	Low	160	148
	High	155	147

[a]Highly susceptible children had DFBETAS scores in the top third of distribution, whereas highly unsusceptible children had scores in the bottom third of the distribution

If the results indicated limited overlap in susceptibility to the two childcare effects, attention was turned to external correlates of DFBETAS' scores, testing the two aforementioned predictions involving family socioeconomic circumstances and child genetic make-up.

Results

Differential susceptibility to quantity and quality of care

The influence scores pertaining to effects of quantity of care on behavior problems and of quality of care on preacademic skills proved unrelated when treated continuously ($r = -0.01$, $p > .05$) and categorically ($X^2 = 0.071$, $p > .05$) (see Table 1). In general, then, knowing that a child was highly susceptible to one influence (e.g., quality:cognition) – or very unsusceptible – was unrelated to his or her susceptibility to the other influence (i.e., quantity–problems). Inspection of Table 1 reveals that in the case of cells with both high and low cross-classifications (i.e., top right, bottom left), approximately 50% of the children categorized as highly susceptible to one of the childcare effects proved to be highly unsusceptible to the other.

The role of family socioeconomic status

To test the hypotheses that (a) the effect of quantity of care on behavior problems would be most pronounced among children from more socioeconomically advantaged families and (b) that of quality of care on preacademic skills would be most pronounced among children from more socioeconomically disadvantaged families, we compared, by means of *t* tests, two groups of children. The first comparison involved children who were and were not highly susceptible to the childcare quantity effect. The second comparison involved children who were and were not highly susceptible to the childcare quality effect on the socioeconomic indicators of maternal years of education and family income-to-needs ratio. Recall that the prediction was that children highly susceptible to the quality-of-care effect would come, disproportionately, from more socioeconomically disadvantaged families and that those highly susceptible to the quantity-of-care effect would come, disproportionately, from more socioeconomically advantaged families.

Inspection of Table 2 indicates, consistent with these hypotheses, that children who proved most susceptible to the effect of quantity of care on problem behavior (i.e., top third of DFBETAS for quantity–problem behavior association) came from families in which, on average, mothers had more years of education and families had more income given family size than those of other children. The data proved inconsistent with the hypothesis that children who were highly susceptible to the effect of quality of care on preacademic skills would be from more disadvantaged families than other children in that the two-group contrasts did not yield significant differences on the dependent variables (although group means did rank in the expected direction) (see Table 3).

Table 2. Mean differences on family socioeconomic indicators of children who were and were not highly susceptible to effect of childcare quantity on problem behavior

	Susceptibility to quantity effect on problem behavior	
	High: $N = 454$	Not high: $N = 910$
Mean years mother's education (*SD*)	14.45 (2.59)	14.12 (2.47)
Difference on mother mean years education	t (866.34) = −2.26, $p = .02$	
Mean family income-to-needs ratio (*SD*, *N*)	3.91(3.00)	3.44 (2.76)
Difference on family income-to-needs ratio	t (799.37) = −2.75, $p = .01$	

Table 3. Mean differences on family socioeconomic indicators of children who were and were not highly susceptible to effect of childcare quality on preacademic skills

	Susceptibility to quality effect on preacademic skills	
	High: $N = 454$	Not high: $N = 910$
Mother mean years education (*SD*, *N*)	14.15 (2.47)	14.27 (2.54)
Difference on mother mean years education	t (633.95) = 1.60, $p = .11$	
Mean family income-to-needs ratio (*SD*, *N*)	3.47 (2.61)	3.66 (2.96)
Difference on family income-to-needs ratio	t (954.06) = 1.19, $p = .24$	

The role of child genotype

To evaluate the potential influence of genotype on susceptibility to childcare effects, we first assigned a score of 2 to children whose susceptibility to each of the two effects was categorized as high (i.e., top tercile), a score of 1 to children who were categorized as high to just one childcare effect, and a score of 0 to children who never proved highly susceptible to a childcare effect. We then conducted a single degree of freedom test of our linear, dose–response hypothesis regarding the association between susceptibility and genetic make-up. Results revealed, consistent with prediction, that the more often a child proved highly susceptible to a childcare effect (i.e., never, once, twice), the higher the polygenic plasticity score (F (1,447) = 10.59, $p < .01$, see Figure 1), although the effect size was clearly small ($R^2 = .025$).

Discussion

Recall that the primary purpose of this inquiry was to examine the utility of using a new, influence-statistic approach to addressing

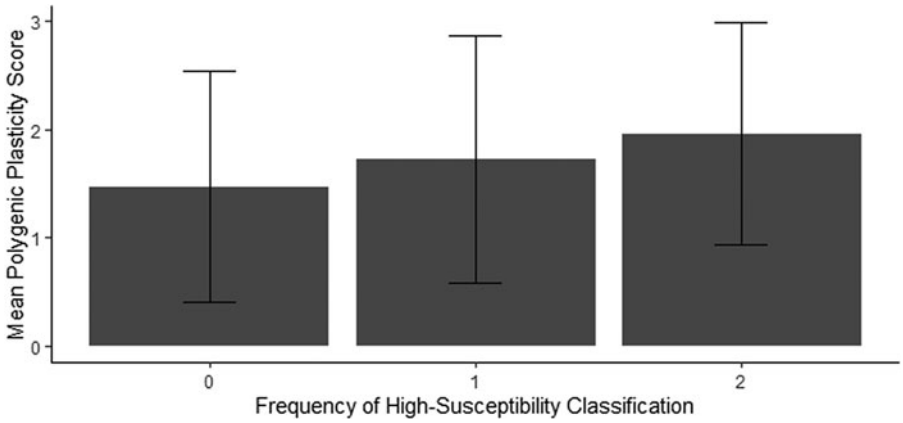

Figure 1. Mean polygenic plasticity score for children categorized as highly susceptible (i.e., top tercile) to effects of both quality on preacademic skills and quantity on problem behavior (2), to effects of only quality or quantity (1), and to neither (0).

what has been an empirically unaddressed issue related to differential susceptibility thinking: are the same – or different – individuals most affected by different environmental exposures? Even as extensive G×E, temperament and physiological research has yielded evidence consistent with differential-susceptibility thinking (Ellis et al., 2011), the answer to this question has remained unclear, even though it has been repeatedly raised (Belsky & Pluess, 2009, 2013; Belsky & van IJzendoorn, 2007). Here, for the first time, we addressed this issue, using well-established findings about childcare effects emanating from the large NICHD study of child care and youth development for illustrative and proof-of-principle purposes.

One not unreasonable concern that might be raised about the influence-statistic approach adopted and the findings it yielded is that the lack of evidence for a general susceptibility trait could be just an artifact of the method itself. That is, no matter what predictor–outcome associations are investigated, lack of consistency in susceptibility – that is, domain specificity rather than domain generality – would emerge empirically. As we were originally concerned about this very issue, we did check this possibility before proceeding to test our hypothesis. As the data presented in Table S2 in the supplementary materials show, this did not prove to be the case. Specifically, the children most highly susceptible to the effects of quality of care on preacademic skills also proved most susceptible to the effect of quality of care on language competence.

Turning to our findings, recall that results revealed that although some children proved consistently susceptible – or not – to the beneficial effects of childcare quality on preacademic skills *and* the adverse effect of quantity of care on problem behavior, this was generally not the case. This evidence of domain specificity led to testing two hypotheses. The first stipulated that children highly susceptible to the effects of quality and quantity of care would come from families that differed socioeconomically. The second predicted that children who proved highly susceptible to both effects, to only one, or to neither would differ systematically – in a dose–response manner – on a polygenic score presumed to reflect developmental plasticity in response to environmental conditions. Recall that the second prediction and part of the first received empirical support.

Perhaps what is most important to appreciate about these findings is that they are "topic specific," perhaps even study specific. Because this inquiry was designed to evaluate whether – and perhaps why – some children proved highly susceptible to effects of quality of care whereas others proved highly susceptible to quantity of care ones, it cannot be concluded that the domain specificity chronicled herein can be generalized beyond the particular focus on childcare effects at age 4.5 years in the NICHD study. Nevertheless, what the current inquiry does indicate, most worthy of note, is that directional and weighted influence statistics like those used herein would appear to be a viable and productive approach to investigating differential susceptibility to distinct experiences and exposures. After all, it would seem difficult to explain why our three-gene, polygenic score successfully distinguished children who systematically varied in their susceptibility to the environmental conditions under investigation if our influence-statistic's approach was not fit for the task at hand. The same would seem to be the case with respect to the finding that children who proved most susceptible to the effect of quantity of care on behavior problems came from more advantaged families than did those who proved less susceptible. All this is not to say, however, that the approach adopted here is – or should be – the only means of investigating domain specificity–generality of environmental influences. Nevertheless, we hope our work encourages others to try the method we implemented.

In further considering our results, we were not entirely surprised by our failure to find support for the hypothesis that it would be children from socioeconomically disadvantaged who benefited the most in terms of their pre-academic skills as a result of exposure to high-quality childcare. This was because the NICHD study included only a limited number of extremely poor and socioeconomically disadvantaged children, even if its sample was more demographically diverse than many have claimed (i.e., not just a middle-class sample). While this feature of the sample may have been reason not to advance the hypothesis we did, we believed it was still worth testing using our influence-statistics' data. In light of the null results, it is worth recalling the adage that "absence of evidence is evidence of absence."

Turning to our second prediction regarding children's genetic make-up, it would be a mistake to assume that the three genes we chose, a priori, to comprise our polygenic score are the most important ones when studying differential susceptibility to environmental influences. Recall that we selected *5-HTTLPR* (short alleles), *DRD4* (7-repeats) and *BDNF* (met alleles) because they were available in the NICHD study data set and had been among those polymorphisms most often found to moderate environmental influences in differential-susceptibility-related fashion in prior G×E work (for reviews, see Belsky & Pluess, 2009, 2013; Belsky & van IJzendoorn, 2017; Ellis et al., 2011). It would seem especially interesting that even though, for the most part, different children proved highly susceptible to the two childcare effects that we investigated, they generally shared

the same genetic make-up, scoring higher than others on our polygenic score. To be appreciated, of course, is that the detected effect size was small, explaining only 2.5% of the variance, a result not out of line with findings from candidate-gene studies. To our way of thinking, effect size was less important than the proof-of-principle result proving to be in the expected direction and to a statistically significant extent. We can imagine that future work will also yield evidence that different polygenic scores composed of different genes might help to account for different contextual effects, especially if polygenic scores are based on many, many polymorphisms. For this reason it is especially important not to reify the polygenic score used herein or presume that it will always be the case that even when different children are affected by different experiences and exposures, this will be for the same genetic reasons.

Despite evidence that the children who scored highest on our polygenic plasticity index proved most susceptible to effects of both of the childcare effects under investigation, it is not entirely clear why some children with similar polygenic scores proved quite different in terms of the childcare effect to which they proved most susceptible. While those most susceptible to the effect of quantity of care on problem behavior were disproportionately likely to score high on the polygenic plasticity score and come from somewhat more advantaged families, exactly why other children with similar polygenic scores proved especially susceptible to the quality of care effect remains to be determined. Because results failed to support the prediction that the latter would be from more disadvantaged families than children who proved less susceptible to this effect, we are left lacking a strong, evidence-based hypothesis as to what other factor(s) might help to account for why some apparently genetically susceptible children benefited cognitively more than others when they experienced high-quality childcare.

Limitations and Future Directions

Whatever the strengths of the research reported herein, it is not without limits. Perhaps most important are (a) its narrow empirical focus – on just two, well-established childcare effects – and (b) consideration of only three polymorphisms. Needless to say, then, future work should seek to move beyond this proof-of-principle effort to examine the potential utility of an influence-statistic approach to investigating what could be described as "differential, differential susceptibility."

It needs to be appreciated that our focus on two different childcare effects – involving different environmental predictors *and* developmental outcomes – is only one of many ways that future work might proceed. Indeed, it will be especially important to build on the current effort by investigating "differential, differential susceptibility" when using (a) the *same* environmental parameter to predict *different* developmental phenotypes, (b) *different* environmental parameters to predict the *same* developmental phenotype (as in Table S2 in the supplementary materials), and (c) a *combination* of the two preceding approaches.

Supplementary Material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579420002205

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