




Human milk immune factors, maternal nutritional status, and infant sex: The INSPIRE study

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Abstract

Objectives: Breastfeeding is an energetically costly and intense form of human parental investment, providing sole-source nutrition in early infancy and bio-active components, including immune factors. Given the energetic cost of

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lactation, milk factors may be subject to tradeoffs, and variation in concentrations have been explored utilizing the Trivers-Willard hypothesis. As human milk immune factors are critical to developing immune system and protect infants against pathogens, we tested whether concentrations of milk immune factors (IgA, IgM, IgG, EGF, TGF β 2, and IL-10) vary in response to infant sex and maternal condition (proxied by maternal diet diversity [DD] and body mass index [BMI]) as posited in the Trivers-Willard hypothesis and consider the application of the hypothesis to milk composition.

Methods: We analyzed concentrations of immune factors in 358 milk samples collected from women residing in 10 international sites using linear mixed-effects models to test for an interaction between maternal condition, including population as a random effect and infant age and maternal age as fixed effects.

Results: IgG concentrations were significantly lower in milk produced by women consuming diets with low diversity with male infants than those with female infants. No other significant associations were identified.

Conclusions: IgG concentrations were related to infant sex and maternal diet diversity, providing minimal support for the hypothesis. Given the lack of associations across other select immune factors, results suggest that the Trivers-Willard hypothesis may not be broadly applied to human milk immune factors as a measure of maternal investment, which are likely buffered against perturbations in maternal condition.

1 | INTRODUCTION

The composition and abundance of human milk immune factors are known to be reflective of a mother's environmental conditions, including her physical environment (Peroni et al., 2010), geographical location (Amoudruz et al., 2009; Holmlund et al., 2010; Munblit et al., 2016; Ruiz et al., 2017), subsistence strategy (Klein et al., 2018), and microbial exposure (McGuire et al., 2021; Prentice, Watkinson, et al., 1984; Tomićić et al., 2010). Human milk immune factors are also associated with a variety of maternal and infant characteristics including delivery mode (Groer et al., 2004; Striker et al., 2004), gestational age (Castellote et al., 2011), mastitis (Castro et al., 2022; Espinosa-Martos et al., 2016; Hassiotou et al., 2013; Hunt et al., 2013; Prentice et al., 1985), time postpartum (Ballard & Morrow, 2013; Czosnykowska-Lukacka et al., 2020; Goldman et al., 1983; Moles et al., 2015; Munblit et al., 2016; Prentice, Prentice, et al., 1983; Turin & Ochoa, 2014), pasteurization method (Escuder-Vieco et al., 2018; Espinosa-Martos et al., 2013), and infant illness (Breakey et al., 2015; Bryan et al., 2007; Hassiotou et al., 2013; Riskin et al., 2012). Maternal diet (Böttcher et al., 2008; Urwin et al., 2012) and nutritional status (Lu et al., 2018; Miranda et al., 1983) are also frequently associated with variation of immune factor concentrations in milk.

Reflecting local ecology (Klein et al., 2018), human milk is thus uniquely suited to prime newborns for their environment (Andreas et al., 2015; Brandtzaeg, 2003). In the early postpartum period, a time when infants' immune systems remain naive (Ballard & Morrow, 2013), mothers transfer immunity to their infants via the provision of colostrum and milk (Andreas et al., 2015; Brandtzaeg, 2003). Lactation, however, is an energetically costly form of parental investment (600 kcals per day; Butte & King, 2005; Lunn, 1994) which involves diverting available energy away from maternal needs to the synthesis of milk for the offspring, an investment that can span several months to years (Valeggia & Ellison, 2001). Therefore, lactation and the composition of human milk are likely subject to energetic tradeoffs and may be responsive to proximate cues in the environment and from the mother-infant dyad.

1.1 | Evolutionary approaches to human parental investment and human milk composition

Evolutionary approaches examining how parental investment may interact and influence human milk composition (e.g., Fujita et al., 2019; Powe et al., 2010) have typically centered on whether there are associations