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Original article

Early Introduction of Solid Foods in Infant's Nutrition and Long-Term Effects on Childhood: A Systematic Review

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Abstract

Background: Early solid food introduction in infancy has been related with some long-term outcomes in childhood, such as high BMI, obesity, diabetes type 1, feeding difficulties andF2-isoprostanes in urinary. ***Methods:*** The purpose of this systematic review is to provide the long-term effects of the early introduction of complementary foods in childhood, independently of breastfeeding or formula-feeding. ***Methods:*** Twelve research studies from Google Scholar, PubMed, and Crossref were added in the systematic review from a total of 1517 articles. ***Results:*** Most studies have shown an association between the introductions of solids before 4 months of age and long-term outcomes in children. However, late introduction of solids may have the same effects as early. Moreover, the role of breastfeeding, which acts protectively in the food transition, is emphasized. ***Conclusions:*** The most appropriate age for introduction in solids is the period of 6 months with continued breastfeeding according to the international guidelines.

Keywords: ***Early introduction of solids; infant's nutrition; exclusive breastfeeding and solid foods; childhood obesity; type 1 diabetes and infant's nutrition; long-term effects of infant's diet.***

1. Introduction

The effects of solid food intake on infant nutrition and their long-term health effects have been debated by many researchers over time. Although breastfeeding accompanies many advantages to the health and general development of children [1-4], beyond the age of six months it is necessary to add complementary foods to provide enough nutrition to infants [5], and this transition is referred to as complementary feeding. According to the World Health Organization (WHO), if complementary foods are not introduced around the age of 6 months or if they are given unsuitable, the development of a child may be delayed [5]. Early introduction of complementary foods increases the probability of immediate effects on infants, such as diarrhea, infections and food allergies [6,7], while the long-term outcomes including metabolic and other diseases are still being investigated.

Exclusive breastfeeding which has the best long-term health effects, is associated with development of a healthy microbiome [8]. Although six months of exclusive breastfeeding may be recommended for most children, complementary foods are aimed to "supplement" continued breastfeeding with those nutrients whose intake has become limited or insufficient [9]. Continued breastfeeding beyond six months contributes to the favorable colonization of the infant's intestine, as it provides protective factors when complementary feeding begins [10]. However, there is little data on the health effects of exclusive breastfeeding that is prolonged beyond the first 6 months, without the introduction of solid foods. For example, in a prospective study between infants who were exclusively breastfed after the first 6 months of age and infants who were on a diet supplement after 6 months, there was a delay in the development of infants in the first group, who experienced a delay associated with inadequate energy intake and certain nutrients [11]. Infant's vitamin D, iron, zinc requirements cannot be met by breastfeeding alone. The risk of iron deficiency anemia at 6 months of age is increased by birth weight, male gender, and weight gain above the reference value from birth [12]. Iron deficiency anemia is a major risk factor for long-term effects on motor, mental and social development in childhood [13,7]. In addition, rickets as a deficiency of vitamin D and a lack of zinc is observed in infants with nutritional deficiencies in complementary nutrition after 6 months [14,15]. However, in low-income countries, breastfeeding can prevent the growth decline associated with the transition from exclusive breastfeeding to complementary feeding, procured that breastfeeding continues and that hygiene and complementary food setting are adequate [16,17]. However an older study on the introduction of solids in infants [18], showed that compared to infants fed complementary foods <6 months under optimal feeding conditions, exclusively breastfed infants have similar developmental and morbidity outcomes. Of course, the majority of the older studies did not find evidence of benefits from the introduction of complementary foods <6 months, nor risks associated with morbidity or weight change [19].

On the other hand, the previous WHO recommendation for infant nutrition stated that infants should be exclusively breastfed from the start of their life to 4 ± 6 months of age [20]. Nevertheless, the WHO's current recommendations for infant nutrition are primarily aimed at reducing morbidity in developing countries [21], based on the findings of a research which concluded that infants who are exclusively breastfed for 6 months are less likely for incidence of gastrointestinal infection than those who are partially breastfed for 3 or 4 months and have not been shown to have developmental deficiencies between infants from either developing or developed countries who are exclusively breastfed for the first 6 months or later [22] .The American Academy of Pediatrics [23] and WHO [24,25] recommend that complementary foods be entered around 6 months of age. If complementary foods are not introduced around the age of 6 months or if they are given inappropriately (before 4 months of age), the development of an infant may be delayed. However, the introduction of food before the age of 4 months is not recommended [26]. However, in 2008, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), recommended that the solid foods should not be introduced before 17 weeks and not after (26 weeks of infant's life) [27].

Although there is almost worldwide accordance that complementary feeding should not commence before 4 months of age, there is a discrepancy about the period of 4-6 months. In addition, while there is considerable research into childhood obesity [28,29] and type 1 diabetes [30,31] and feeding difficulties that appears to be related to early introduction of solids in infants. Regarding diabetes type 1, because the genetic background is stable, the increase in cases recommends the contribution of some environmental factors to its development during childhood. More specifically, it has been found that infant nutrition can contribute to the development of islet autoimmunity Exclusive breastfeeding and vitamin D supplementation in infancy are reported to provide a protection against beta cell autoimmunity and diabetes type 1. In contrast, the first exposure to cow milk proteins and cereals and the high birth weight have been implicated as risk factors for diabetes type 1 [32]. Regarding the risk of obesity in children, the early introduction of food has been also blamed, while breastfeeding seems to be a protective factor [33]. Furthermore, early food introduction can even affect eating behavior in terms of eating preferences in the later life of the infant. So, feeding difficulties have been observed in children who have undergone early solid food intake. Thus, infants who were late (10 months and older) to be inserted into the bumps were more likely to feeding difficulty had more specific likes and dislikes later [34]. More specifically, the long-term outcomes in childhood include mainly metabolic disorders and other problems [35]. So, the purpose of this review is to provide the long-term effects of the early introduction of complementary foods in childhood, independently of breastfeeding or formula-feeding.

2. Materials and Methods

The study was not registered to PROSPERO. The aim of this study was to investigate the long-term effects of early introduction of complementary foods in childhood. In particular, we investigate the introduction of solid foods to infants, regardless of the presence of breastfeeding. The research was carried out based on Google Scholar, PubMed/Medline and Crossref according to PRISMA guidelines for systematic reviews and meta-analyses [36,37].

The keywords used were as follows: introduction of solid foods OR introduction of complementary foods AND long-term health outcomes; introduction of solid foods OR introduction of complementary foods AND obesity in childhood OR overweight in childhood; introduction of solid foods OR introduction of complementary foods AND diabetes type 1 in childhood OR metabolic outcomes in childhood; introduction of solid foods OR introduction of complementary foods AND chronic diseases OR problems OR difficulties in childhood.

2.1. Inclusion and exclusion criteria

We included cross-sectional, case controls, observational and cohort studies that evaluated the correlation between early introduction of solid foods and long-term outcomes in childhood. We excluded studies that were review articles (systematic or meta-analyses), included health outcomes in adulthood, papers that did not report a statistical results between early introduction of solids and long-term outcomes and finally, articles written in other language than English.

In order to reflect recent complementary feeding, only studies published between 2011 and 2021 were considered. The search was performed from January 2022 to April 2022 and the results of this search were confirmed by another author of the research team to validate their reliability. So, from 1529 articles; the 12 were comprised in the systematic review. The studies were evaluated firstly by their titles and abstracts. The full texts of the research papers were evaluated against the exclusion and inclusion criteria and from139 articles,120 systematic reviews, reviews, and meta-analyses were excluded, as well as 7 articles written in another language han English (**Figure 1**). The study presents as exposure, the early introduction of solid foods in infant's nutrition and as an outcome, the long-term effects of this exposure on children's health. As an early introduction we mean all solid or liquid foods (juices or infusions) that can be given to the infant other than breastfeeding or formula-feeding before 6 months of age. As an outcome, we analyzed some health problems, such as overweight and obesity; feeding difficulties; metabolic disorders and diabetes type 1 in childhood. These outcomes were substantiated by the necessary clinical examinations depending on each problem. For example, Type 1 diabetes was evaluated by a clinician and defined as classic symptoms of polyuria and polydipsia with a glucose level of ≥200 mg/dL or an oral glucose tolerance test with fasting plasma glucose of ≥126 mg/dL or a 2-hour glucose of ≥200 mg/dL. The obesity defined by using the cut-off values for body mass index (BMI) by gender and age established by the International Obesity Task Force (IOTF)for children and adolescents in 2000 [38]. The F2-isoprostane concentrations in childhood (on average, (0.10 ng/mg per month of age at introduction) are the lower level. The data regarding feeding difficulties collected from a questionnaire which collected the number of cases of infant's meals per day their dietary.

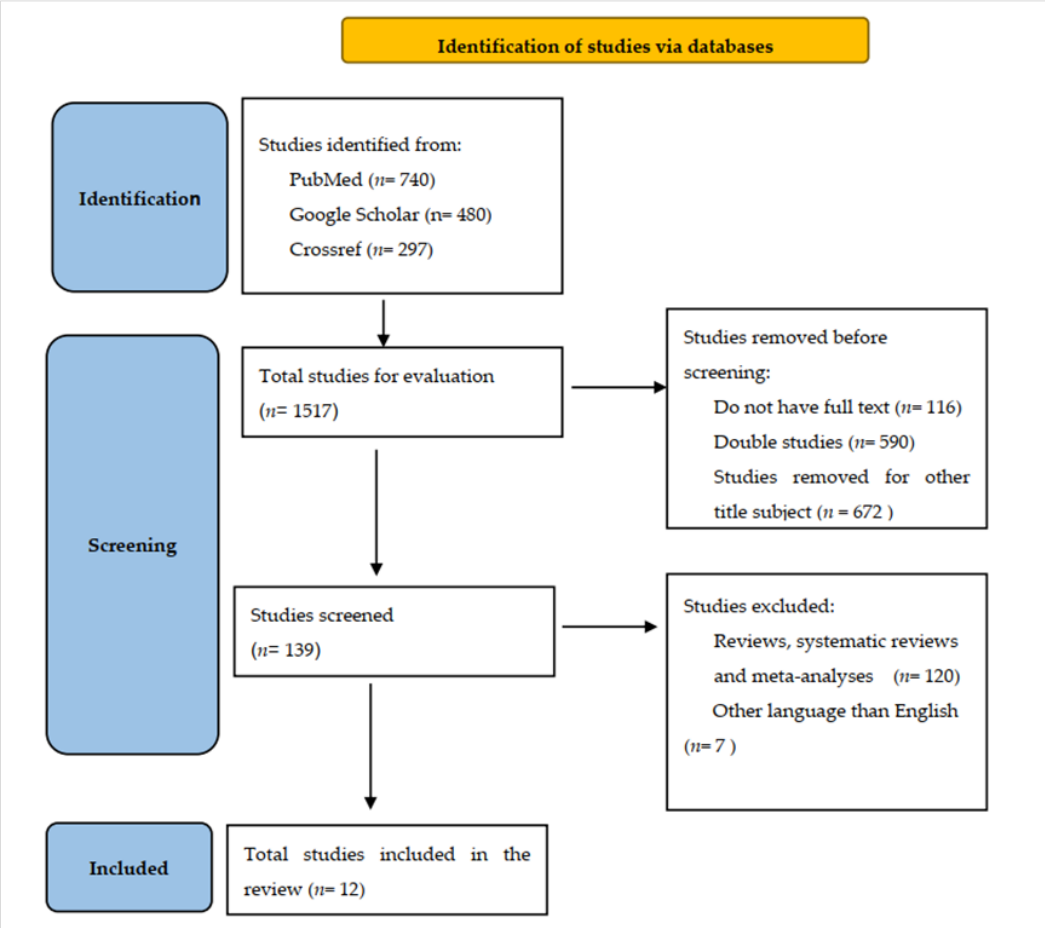

Figure 1. Flow chart: structure search strategy according to PRISMA

2.1. Methodological quality of the included studies

Concerning the quality of the studies, three groups of criteria were used to value them. The first group (Selection) consists of 4 criteria. The first group of criteria, regarding the representative exposure sample, was met by all articles. The second group of criteria evaluated the selection of non-exposure, i.e., we did not know previously which infants were exhibited to early introduction of solid foods, was met in all articles. All studies met the third group of criteria (concerns whether there were exhibition findings), because the exposure was recognized by the determinate examination tests. In almost all articles (except two), the outcome did not precede the study (the long-term effects on childhood were the final result of each study).

The second group of criteria (Comparability) involves of 2 parameters concerning adjustment for confusing factors. However, the first criterion which was the adaptation for the educational status of mothers was met by the majority of studies. In all articles, an adaptation for an additional confounding factor had been applied.

The third group of criteria (Results) consists of 3 parameters, assessing the quality of the results of each article. All articles met the first criterion for assessing the long-term outcomes of early introduction of solid foods on childhood with appropriate examination tests. In all prospective and cohort studies there was adequate follow-up time, thus the cross-sectional studies did not fulfill the second criterion. Finally, all studies met non-bias of wear, the third group of criteria. The total score of articles varied between 7 and 9 (**Table 1**).

Table 1: Methodological quality of the included studies

Author/Year	Selection 1 2 3 4	Comparability 1 2	Result 1 2 3	Total
1. Virtanen (2011) [32]	* * * *	* *	* * *	9
2. Huh (2011) [39]	* * * *	* *	* * *	9
3. Zhou (2011)	* * * -	* *	* - *	7
4. Joseph (2011) [41]	* * * *	* *	* * *	9
5. Frederiksen (2013) [42]	* * * *	* *	* * *	9
6. Gishti(2014) [43]	* * * *	* *	* * *	9
7. Frederiksen (2015) [44]	* * * -	* *	* * *	8
8. Sun (2016) [45]	* * * *	- *	* - *	7
9. Hollis (2016) [46]	* * * *	* *	* * *	9
10. Papoutsou(2017) [47]	* * * *	* *	* * *	9
11. Pluymen (2018) [48]	* * * *	* *	* * *	9
12. Schneider (2020) [49]	* * * *	* *	* * *	9

Notes: The group criteria were 1. Selection: a) Representative exposure sample, b) selection of non-exposed, c) exposure finding, d) outcome did not precede the study. 2. Comparability: a) adaptation for educational level, b) adaptation for additional confounding factor. Results: a) outcome evaluation, b) adequate monitoring time, c) non-bias of wear. The symbol (*) means that the study met the specific criterion and the symbol; (-) means that the study did not meet it.

3. Results

The 12 articles in this study were carried out in different countries. Eight were prospective or cohort studies, 2 studies were cross-sectional, 1 study was longitudinal observational and 1 was a case control (**Table 2**). Regarding the methodological evaluation of the articles, 10 studies were very strong and 2 were of moderate quality (**Table 1**). In particular, the research of Virtanen [32], which was carried out in Finland, all available information support an association between the introduction of root vegetables at the age of 4 months and type 1 diabetes, independently of the introduction of other nutrition and of some putative socio-demographic and perinatal confounding factors. In more details, early introduction of potatoes and carrots in infancy was strongly related to advanced ß-cell autoimmunity during the whole follow-up period. The mean period of breastfeeding of those children was 1.4 months. The Huh cohort study [39] highlights the negative outcome of early introduction of solid foods on infants, on the development of obesity at the age of 3. In formula-fed infants who were never breastfed or who paused breastfeeding before the age of 4 months the intake of solids before the age of ≥4months was linked with a sixfold increase in the risk of obesity later (3 years of age). Among infants who were breastfed for 4 months, the timing of the introduction of solid foods was not associated with obesity. The case-control study of Zhou [40] aimed to investigate the link between early introduction to solid foods and other perinatal factors with obesity in childhood. However, the results show that the presence of fetal macrosomia, fetal musical education and cesarean delivery constitute risk factors for obesity in childhood. Furthermore, the introduction of solid foods before the age of 4 months was a major risk factor for this situation in childhood. The cohort study of Joseph [41] investigated the relationship between introduction of complementary foods <4 months and Immunoglobulin E (IgE) to peanut, milk and egg, allergen at 2-3 years. In this study, 594 infant-maternal pairs were analyzed and according to the results, early introduction of solids in infants who were breastfeeding reduced the risk of peanut sensitization among infants with a parental history of allergies. Despite that, avoidance of food allergy through dietary manipulation remains challenge. In addition, the study of Frederiksen, published on 2013 [42] investigated the links between perinatal exposures, especially early introduction of solids and the development of Type 1 diabetes. The results show that both early and late first exposure to any solid food predicted development of Type 1 diabetes. Specifically, early exposure to fruits and late exposure to rice or oat, predicted Type 1 diabetes, while breastfeeding at the time of exposure to wheat/barley remained protective. However, more breastfeeding months marginally decreased the risk for Type 1 diabetes. The cohort of Gishti [43] investigated the associations of breastfeeding exclusivity and duration and age at introduction of solid foods with, C-peptideand insulin blood lipids and risk of grouping of cardio-metabolic risk factors. The results of 3417 children show that early introduction of solid foods was associated with higher levels of total cholesterol levels in blood. Breastfeeding was not associated with childhood blood levels of lipids but was associated with higher C-peptide concentrations and insulin. Thus, whether infant diet constitution affects metabolic disorders in childhood should be further investigated.

Table 2: The included studies characteristics

Author/ Country	Design	N	Data	Exposure	Outcome	Outcome age	Exposure Effect
1. Virtanen (2011) [32] Finland	Cohort study	6069 infants with HLA-DQB-conferred susceptibility to Type 1 diabetes	3 university hospitals in Finland	Introduction at the age of 4 months of root vegetables	Type 1 diabetes	3 years	Aggravating in infants with HLA-DQB
2. Huh (2011) [39] USA	Cohort study	847 children	Project Viva	Introduction of solid foods at <4, months of age	Obesity	3 years	Aggravating in formula-fed infants
3. Zhou (2011) [40] China	Case-control study	162 children (81 couples)	10 kindergarten schools in China	1. Introduction of solid foods< age of 4 months, 2. Cesarean section 3. Macrosomia 4. Fetal musical education	Obesity	3-6 years	Aggravating
4. Joseph (2011) [41] USA	Cohort study	594 infant-maternal pairs	Hospital and Medical College of Georgia	Introduction of complementary food (egg, milk, peanut) <4 months	Allergies	2-3 years	Protective in children with a parental history of asthma or allergy
5. Frederiksen (2013) [42] USA	Longitudinal observational study	1835 children at increased genetic risk for Type 1 diabetes	Hospital in Colorado	1.Early (<4 months of age) and late (≥6 months of age) first exposure to solid foods 2. Complicated vaginal Delivery	Type 1 diabetes	2 years	Aggravating in infants with increased genetic risk forType 1 diabetes
6. Gishti (2014) [43] Netherlands	Cohort study	3417 children	Generation R Study, Rotterdam	1. Breastfeeding durationand exclusivity 2. Introduction of solid foods <4 months	Metabolic disorders	Mean age 6 years	No consistent associations of infant feeding patterns with metabolic outcomes at schoolage

7. Frederiksen (2015) [44] USA	Cohort study	328 Childrenat increased genetic risk for developing T1D. F2 -isoprotanes	The DAISY cohort	Introduction of solid foods <4 months	Urinary F2 -isoprostane concentrations	Under 11.5 years	Aggravating in infants who were not breastfeeding
8. Sun (2016) [45] Australia	Cross-sectional study	3153 Infants	The HealthNuts study	1.Males 2.Higher birth weigh 3. Younger age of mother 4.Mother's smoking 5. Introduction of solids <4 months	High BMI	1 year	Aggravating mainly in infants who were not breastfeed >4 moths
9. Hollis (2016) [46] UK	Cohort study	2389 Mother-child pairs	Southampton Women's Survey (SWS)	Introduction of solids <4 months	Feeding difficulties	3 years	Aggravating
10. Papoutsou (2017) [47] 8 European countries	Cross-sectional study	16228 Children	The IDEFICTS study	1. Introduction of solids <4 months 2. Introduction of solids ≥7 months	Overweight /obesity	2-9 years	Aggravating in infants who were not breastfed exclusively
11. Pluymen (2018) [48] Netherlands	Cohort study	2611 children	The PIAMA study	Introduction of solids <4 months	Overweight	1-17 years	Aggravating in infants who were not breastfed exclusively >4 months
12. Schneider (2020) [49] Brazil	Cohort study	3823 (2004c) 3689 (2015c) children	Pelotas 2004 and 2015	1. Introduction of solids <6 months 2. males	Overweight	2 years	Aggravating in infants who were not breastfed exclusively >6 months

* Notes: The HLA-DQB1 gene gives directions for making a protein that plays a critical role in the immune system. The HLA-DQB1 gene is part of a family of genes called the human leukocyte antigen (HLA) complex. Urinary F2 -isoprostane concentrations is an indicator of oxidative stress.

The cohort study of Frederiksen published in 2015 [44], evaluated the connection link between timing of solid food introduction and F2-isoprostanes in urinary a marker of oxidative stress. Oxidative stress has been linked to many diseases, but little information subsists on biomarkers of oxidative stress on children's health. The researchers reported that childhood F2-isoprostane concentrations were, on average, 0.24ng/mg lower in infant's breastfed at solid food starting compared with those who were not. In more details, being stared to solid foods before 4 months of age and not being breastfed at the time of the beginning of solids was crucially associated with increased F2 -isoprostane concentrations in contrast with the introduction to solid foods between 4 and 5 months of age. Therefore, the subsequent introduction of solid or complementary foods and breastfeeding during the introduction of solid foods proposed a long-term protective effect against increased concentrations of F2-isoprostane throughout childhood. The cross-sectional study of Sun [45], investigated the links between breastfeeding duration, age at the introduction of solid foods, and their interplay in relation to infant BMI. However, from 3153 infants, 147 have an above normal BMI. In contrast with infants with a normal BMI, those with an above normal BMI were more likely to have a higher birth weight and to be male, and those mothers more likely to be at younger age. Furthermore, infants fully breastfed for 4 to >12 months were less likely to have an above normal BMI, in conflict with those fully breastfed for 0 to 1 month. In addition, the early introduction of solid foods <4 months resulted in increased chances of high BMI, independently of infants' breastfeeding status. Introduction of solids >4 months may be associated with high BMI in infants fully or partially breastfed for <4 months, but not in infants breastfed for ≥4 months.

In the cohort study of Hollis [46], the authors purposed to determine whether age at the solids intake was associated with feeding difficulties in a sample of 2389 mother–child pairs. The results of this study show that infants who were introduced to solids between 4 and 6 months had a higher risk of feeding difficulties than infants who were entered to solids ≥6 months. The cross-sectional study of Papoutsou [47], published in 2017, shows that infants who were not breastfed exclusively for 6 months and were introduced to solids while breastfeeding continuing until the first year or more, were less likely to be overweight/obese at the age of 2 to 9 years. More specifically, the results revealed that infants who discontinued exclusive breastfeeding <4 months and then were introduced to solids were more likely to became overweight/obese in childhood. On the other hand, late introduction of solids at≥7 months among breastfed infants was also associated with overweight/obese in childhood. This research highlights the catalytic role of breastfeeding on the introduction of solids to prevent overweight. A recent cohort study published by Pluymen [48] investigated whether early introduction of complementary foods is linked with an increased risk of overweight in childhood. The results of this study show that formula-fed infants and infants who were breastfed for <4 months, but not infants who were breastfed for >4 months, had a higher risk of being overweight later in childhood. These data were different for children introduced to solids >4 months of age. Therefore, in this study supports the catalytic role of breastfeeding on the introduction of solids to prevent overweight, as well. Finally, in a recently published article by Schneider [49], which investigated the introduction of complementary feeding in childhood, we see that the risk of overweight increased 1·66 and 1·50 times with the early intake (<6 months) of solids. In more details, the present study had the peculiarity of examining longitudinal differences in complementary feeding practices during the first year of age in two large birth cohort studies 11 years apart and with high follow-ups. However, in 2015c the prevalence of the risk of overweight children was higher in boys than in girls but, the prevalence of the risk of overweight was higher in girls who were introduced to fluids, semi-

solids or solids <6 months in contrast to boys. In 2004c, no statistically significant correlation was observed between the early introduction of complementary feeding and the risk of being overweight at 24 months. Nevertheless,11 years later, infants who received fresh or powdered milk plus water, teas or juices and infants who were fed with fresh or powdered milk plus semi-solid or solid foods (liquid or not), had a higher risk of being overweight at 2 years, respectively, in contrast to infants who did not.

4. Discussion

The aim of our systematic review was to provide the long-term effects of the early introduction of complementary foods in childhood, independently of breastfeeding or formula-feeding. The present study provides a strong link between early introduction of solids in infant's nutrition and obesity or overweight, Type 1 diabetes, feeding difficulties and Urinary F2 -isoprostane concentrations. The findings, according to the included articles, show that solid food intake time is essential for the further health in childhood but seems to be influenced by other factors. Particularly in cases with diabetes Type 1, the introduction of oat root vegetables at the age of 4 months and [32] or earlier introduction of solids (<4 months) [42] may increased the risk of Type 1 diabetes, in infants at increased genetic risk for diabetes. Also, the introduction of solid foods after the age of 6 months seems to have the same effect on these children, as in the early introduction. Therefore, for the prevention of Type 1 diabetes, the most appropriate age for solid food intake is 6 months according to the Center for Disease, Control and Prevention (CDC) [50], UNICEF [51] and WHO [24]. Concerning the prevention of overweight/obesity, the majority of included studies have shown that the introduction of solids before the age of 4 months causes negative effects on childhood [39,40,45,47-49], but there is evidence that overweight/obesity can be an outcome of a late introduction of solids (≥7 months) [47], as well. However, for the prevention of overweight/obesity, the most appropriate time is 6 months of age. In addition, the duration of breastfeeding can be an important prognostic factor, since children who were exclusively breastfeed during the period of introduction of solid foods were less likely to be overweight or obese. An explanation for this phenomenon is that formula-fed children are more likely to feed on a schedule, resulting usually in high obesity rates [52]. Also, self-regulation of energy introduction might be problematic when exclusive breastfeeding stops early and is substituted by formula milk [53]. In addition, fetal macrosomia or high birth weight predict obesity, especially in male offspring and in infants with short breastfeeding duration [54] and the presence of younger mother age and smoking during pregnancy may be associated with reduced breastfeeding duration [55,56]. Cesarean delivery can also be a prognostic factor for reduced breastfeeding duration and as a result, formula feeding and early introduction of solid foods may occur with all the negative effects [57].

Severe feeding difficulties during childhood were a more frequent sign in infants whowere introduced in solids <4 months. In particular, there is a strong connection link between infants who were not breastfeed >4 months and were introduced in solids with feeding difficulties in childhood [46]. Therefore, infants should be fed solid foods during the 6th month so that there is no aversion to them later. Certainly, long-term protective effect of later solid food introduction and breastfeeding against increased F2 -isoprostane concentrations throughout childhood are well known [44]. It is already known that human colostrum has been shown to have antioxidant and anti-inflammatory properties. So, early and exclusive breastfeeding and introduction of solids at the same time as the continuation of breastfeeding is considered a key factor to avoid negative consequences in childhood. Concerning the protection of allergies in children the conclusions are contrary to all of the above. Thus, the introduction of complementary food (egg, milk, peanut) before 4 months seems to work protectively in preventing allergies in the future. However, exclusive breastfeeding is a major factor associated with a lower prevalence of allergic and infectious diseases in childhood and later in life [58]. As for metabolic outcomes, until now, there is no consistent association of infant feeding patterns with these disorders at school age. Nevertheless, more studies on this area are needed to prove a negative or positive correlation [43].

We can see in the majority of the studies that the effects of solid food intake depend to a large extent on the presence of exclusive breastfeeding up to 6 months of age [3,4]. Particularly, in the prevention of obesity or high BMI, breastfeeding is associated with lower protein intake and better self-regulation of energy intake compared to formula milk. Alike, a link between early introduction of solids and an above normal BMI has been found as introduction association of solids may drive to increased secretion of appetite-stimulating hormones, including ghrelin [59]. According to the above findings, there are potential differences between the early introductions of solid foods in case of breastfed infants versus formula-fed infants. More specifically, several articles highlighted that breastfeeding is a protective factor even for those infants who undergo to early introductions of solids, while continuing to breastfeed [39,44,45,47-49]. On the other hand, formula-fed infants are more burdensome in terms of the long-term effects of early introductions of solids in childhood. Also, in addition to duration, the exclusivity and of breastfeeding, giving a clear lead to infants who are introduced to complementary foods during the 6th month, while exclusively breastfeeding and continue breastfeeding then.

Finally, in the present systematic review, an attempt was made to approximate the month of infant's age that the early introduction of solids may cause various severity long-term outcomes. Most studies have linked the introduction of solid foods before the fourth month of infancy to the appearance of high BMI, obesity, type 1 diabetes (in infants with genetic risk for Type 1 diabetes) and feeding difficulties. Consequently, the period considered most dangerous for the appearance of the above is the period before 4 months of age. The above findings also enhance the beneficial presence of breastfeeding at the time of introduction of solid foods. Indeed, the age of 6 months is the most appropriate period for the introduction of complementary foods, while infants who were exclusively breastfed had several advantages over infants who were not exclusively breastfed in terms of the appearance of health outcomes in childhood.

Strengths and Limitations

This study has some strengths and limitations. First, it is the most recent systematic review of early introduction of solids and the long-term effects on childhood in general. It is also a study, that includes both breastfeeding and non-breastfeeding infants to draw conclusions. However, a limitation of the study is that we used general search terms, so we have no results for other possibly specialized childhood outcomes. Also, no emphasis was placed on the characteristics of the infant's history when reporting the findings, e.g. race / nationality, country of origin, which could limit the substantive interpretation of the findings.

5. Conclusions

Our findings suggest that the optimal practice mainly for overweight, obesity, diabetes type 1, is in direct support of international recommendations for 6 months as the most appropriate age for solids introduction. Also, results may differ between breastfed and formula-fed infants, giving an obvious advantage to infants who exclusively breastfeed for up to 6 months and continue breastfeeding later. However, late introduction of solids may have the same effects as early. Therefore, health care professionals, especially midwives and pediatricians, should emphasize the international recommendations mainly in countries with low rates of

exclusive breastfeeding and high rates of cesarean deliveries. In order to prevent the childhood effects of premature food intake, especially childhood obesity and diabetes type 1, health professionals should emphasize the exclusivity and duration of breastfeeding for at least the first 6 months of infant's life according to the international recommendations. In addition, health professionals need to focus on women who are less likely to follow feeding recommendations or have problems accessing the health system.

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