Rôle de l'alimentation dans la prévention des complications associées à une exposition intra-utérine au diabète gestationnel

Thèse

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Résumé

Les enfants ayant été exposés au diabète gestationnel (DG) *in utero* sont à risque de développer différentes complications de santé plus tard dans la vie, comme l'obésité et le diabète de type 2 (DT2). À ce jour, peu de stratégies visant la prévention de ces complications chez ces enfants ont été identifiées. L'objectif général de mon doctorat était donc d'évaluer le rôle de l'alimentation dans la prévention des complications associées à une exposition intra-utérine au DG.

Plus spécifiquement, le premier objectif de cette thèse était d'évaluer le rôle de l'allaitement maternel dans la prévention de l'obésité. Pour ce faire, l'étude de l'association entre la durée de l'allaitement maternel et la croissance des enfants de 0-5 ans a été évaluée chez des enfants exposés ou non-exposés au DG *in utero*. Ces enfants étaient des participants d'une étude transversale visant à évaluer l'impact du DG sur la santé de la femme et de son enfant, ainsi que de comprendre le rôle des facteurs postnataux dans la prévention des complications associées au DG (étude GDM2). Ensuite, le deuxième objectif de mon doctorat était d'évaluer l'association entre l'état de santé de la femme, y compris son statut de DG, et la composition de son lait maternel en macronutriments, ainsi que d'évaluer l'association entre la composition du lait maternel et la croissance de l'enfant. L'étude de la composition du lait maternel des femmes avec et sans antécédent de DG a pu être réalisée dans le cadre d'une étude pilote d'un projet d'intervention visant la modification des habitudes de vie en période postpartum chez ces femmes (projet DÉPART). Le troisième objectif de mon doctorat était d'évaluer l'association entre le moment d'introduction des jus de fruits 100% purs chez le nourrisson et la consommation d'aliments et de boissons au goût sucré pendant l'enfance chez les enfants ayant participé à l'étude GDM2. Le quatrième objectif était d'évaluer l'association entre la qualité de l'alimentation de l'enfant et son profil anthropométrique et métabolique pendant l'enfance. Finalement, l'étude de certains facteurs individuels et environnementaux associés à la qualité de l'alimentation des enfants exposés ou non-exposés au DG a été réalisée, toujours au sein du projet GDM2, pour compléter les objectifs de cette thèse.

Les résultats de mon doctorat ont permis de déterminer que l'alimentation en période postnatale a le potentiel d'influencer l'association entre le DG et le développement de complications de santé plus tard pendant l'enfance. Plus précisément, l'introduction précoce des jus de fruits chez le jeune enfant serait associée à une plus grande consommation de jus pendant l'enfance au sein de cette population. Ainsi, établir de saines habitudes alimentaires dès le plus jeune âge pourrait aider à améliorer la qualité de l'alimentation de ces enfants à plus long terme, ce qui permettrait de réduire leur risque de complications de santé. En effet, les résultats de cette thèse suggèrent aussi que la qualité de l'alimentation des enfants exposés au DG *in utero* serait associée à une meilleure distribution du tissu adipeux et une plus faible résistance à l'insuline. De plus, la promotion d'un environnement alimentaire favorable à une saine alimentation à la maison, par exemple par la prise de repas en famille ou par une plus grande consommation de fruits et légumes chez la mère, pourrait être une stratégie efficace pour améliorer la qualité de l'alimentation de ces enfants. Finalement, bien que l'allaitement maternel ne fût pas associé à la courbe de croissance des enfants de moins de 5 ans exposés au DG, les résultats de cette thèse ne suggèrent pas non plus d'effet néfaste de l'allaitement sur la croissance de l'enfant en contexte de DG et ce, malgré le fait que la composition du lait maternel soit influencée par le statut de DG de la femme. Ainsi, l'allaitement maternel devrait être encouragé chez ces femmes considérant les nombreux avantages qui y sont associés.

Abstract

Children exposed to GDM *in utero* are at high risk of developing many health problems later in life, such as obesity and type 2 diabetes (T2D). To date, there is a lack of effective preventive strategies for these complications among these high-risk children. Therefore, the aim of this thesis was to evaluate the role of diet in the prevention of complications associated with *in utero* exposure to gestational diabetes mellitus (GDM).

Specifically, the first objective of this thesis was to evaluate the role of breastfeeding in the prevention of childhood obesity. Accordingly, we studied the association between breastfeeding duration and growth trajectory from birth to 5 years among children exposed and unexposed to GDM *in utero*. These children were participants of a cross-sectional study that aimed at studying the impact of GDM on mother and children's health, and to better understand the role of postnatal factors in the prevention of complications associated with GDM (GDM2 study). The second objective of this doctoral project was to evaluate the association between maternal health, including GDM status during pregnancy, and breastmilk macronutrients composition, and to evaluate the association between human milk composition and infant growth. The study of human milk composition among women with and without GDM was conducted in a pilot study of an intervention program that aimed at improving lifestyle habits among women with a history of GDM during the postpartum period (DÉPART study). The third objective of this thesis was to evaluate the association between the timing of fruit juice introduction during infancy and consumption of sweet-tasting foods and beverages during childhood among children that participated in the GDM2 project. The fourth objective was to evaluate the association between diet quality during childhood and anthropometric and glycemic profiles among these children. Finally, the study of several individual and environmental factors that were associated with diet quality of children exposed and unexposed to GDM was conducted among GDM2 participants.

Results from this thesis suggested that nutrition in the postnatal period has the potential to influence the association between *in utero* exposure to GDM and health complications during childhood. More specifically, early introduction of fruit juice during infancy was associated with higher consumption of fruit juice during childhood among children exposed to GDM *in*

utero. Thus, establishing a healthy diet early in life could be a promising strategy to enhance diet quality later in life, which could help reducing subsequent risk of obesity among these high-risk children. Indeed, results from this thesis suggested that a healthy diet during childhood among children exposed to GDM *in utero* was associated with a healthier fat mass distribution and lower insulin resistance. Promoting a healthy food environment at home, for example through family meals or by improving consumption of vegetables and fruits among mothers, could be an effective strategy to improve diet quality of these children. Finally, while breastfeeding was not associated with infant growth between 0-5 years among children exposed and unexposed to GDM, our results did not suggest any negative impact of breastfeeding on children's growth in the context of GDM, even if breastmilk composition could be altered in women with previous GDM. Therefore, breastfeeding should be encouraged among these women given all the proven benefits of this practice.

Table des matières

Liste des figures

Liste des tableaux

Chapitre 8

Chapitre 9

Liste des abréviations

DG : diabète gestationnel

DT2 : diabète de type 2

DT1 : diabète de type 1

ESCC : Enquête sur la santé dans les collectivités canadiennes

FID : Fédération internationale du diabète

HAPO : *Hyperglycemia and Adverse Pregnancy Outcomes*

HEI : Healthy eating index

HGPO : hyperglycémie provoquée par voie orale

IADPSG : *International Association of the Diabetes and Pregnancy Study Groups*

IC : intervalles de confiance

IHAB : Initiative des hôpitaux amis des bébés

IMC : indice de masse corporelle

INAF : Institut sur la nutrition et les aliments fonctionnels

LDL : *Low Density Lipoprotein*

OMS : Organisation mondiale de la santé

OR : *odds ratio*

RR : risque relatif

SWIFT : *Study of Women, Infant Feeding and Type 2 Diabetes after GDM*

TG : triglycérides

UNICEF : Fonds des Nations Unies pour l'enfance

WIC : *Special Supplemental Nutrition Program for Women, Infants and Children*

À papa et maman,

“The future belongs to those who

believe in the beauty of their dreams”

- Eleanor Roosevelt

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La réalisation de mes études de doctorat a été possible grâce à plusieurs personnes, notamment tous les collaborateurs aux projets de recherche présentés dans l'avant-propos de cette thèse. Je les remercie pour leur excellent travail, leur rigueur scientifique et leur précieuse collaboration. Je remercie également Steeve Larouche et Christiane Landry pour leur travail à l'unité clinique, principalement auprès des petits participants de mon projet de recherche.

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Après plus de huit ans à l'INAF, la liste des étudiants et professionnels qui ont embellis mes années d'études est très longue, mais je tiens à remercier tous ceux qui ont croisé mon chemin pour les moments de bonheur partagés ensemble. L'INAF est sans aucun doute le meilleur milieu de recherche et de travail qui soit, notamment grâce à vous. C'est d'ailleurs ici que j'ai rencontré plusieurs de mes amies pour la vie. Maude, Marie-Ève, Jessica et Stéphanie, les années à la maîtrise en votre compagnie ont été merveilleuses et je me sens privilégiée de partager mon quotidien avec vous encore aujourd'hui. J'ai l'impression que vous avez réalisé une partie de mon doctorat avec moi. Merci pour votre soutien et votre amour inconditionnel!

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Avant-propos

Cette thèse contient six articles scientifiques que j'ai rédigés dans le cadre de mon doctorat pour lesquels je suis première auteure. Le premier article présenté au chapitre 4 est une revue systématique de la littérature. Aux chapitres 5, 7, 8 et 9, les articles présentent des résultats issus d'une étude transversale réalisée chez des femmes avec et sans antécédent de DG et leurs enfants (étude GDM2). Les résultats de l'étude présentée au chapitre 6 sont des résultats issus d'un projet pilote d'une intervention visant la modification des habitudes de vie en période postpartum chez des femmes ayant eu une grossesse compliquée par un DG (projet DÉPART).

Ma directrice de doctorat, Dre Julie Robitaille, est la chercheuse principale des différents projets de recherche présentés dans cette thèse. Elle a supervisé l'ensemble de mes travaux de doctorat, autant pour les rencontres auprès des participants que pour la rédaction des articles scientifiques. Elle a contribué à l'élaboration des objectifs de ma thèse ainsi qu'à l'analyse et l'interprétation des résultats qui y sont présentés. L'expertise en pédiatrie de ma co-directrice, Dre Isabelle Marc, a été utile à l'analyse et à l'interprétation des résultats présentés dans ma thèse.

Pour la revue de la littérature présentée au chapitre 4, l'aide de la bibliothécaire conseil Gabriela-Magdalena Sofian a été sollicitée pour élaborer la stratégie de recherche systématique de la littérature. Daniela Zavala Mora, une autre bibliothécaire conseil de la Faculté des sciences de l'agriculture et de l'alimentation, était aussi en soutien à mes questions lors de la rédaction de la revue. Mon rôle pour cet article a donc été d'élaborer la stratégie de recherche avec Gabriela-Magdalena Sofian, de lancer cette stratégie dans trois bases de données, d'importer les articles résultant de la recherche dans le logiciel *Covidence*, d'effectuer la révision des titres, résumés et articles à inclure dans la revue, d'élaborer le tableau d'extraction des données et le compléter, d'évaluer la qualité des études inclues et de rédiger l'article. Mélissa Bélanger a contribué significativement au processus systématique de la revue en étant la deuxième réviseure des titres et résumés ainsi que des articles à inclure dans la revue. Julie Robitaille, était disponible en cas de désaccord entre les deux réviseurs lors du processus de sélection des articles et de l'extraction des données. Tous les coauteurs ont révisé le manuscrit.

Chapitre 4 : Dugas C, Bélanger M, Robitaille J. Role of breastfeeding in obesity prevention in children born from mothers with gestational diabetes mellitus: a systematic review. Cet article a été soumis pour publication à la revue *Childhood Obesity* le 30 août 2021.

Dans le cadre du projet GDM2, j'ai contribué au recrutement, aux rencontres des participants et à la collecte et saisie des données alors que j'étais auxiliaire à la recherche pendant mon baccalauréat et pendant ma maitrise en nutrition. Lors de mon doctorat, j'ai réalisé les analyses et l'interprétation des données et j'ai rédigé les articles scientifiques présentés dans cette thèse. Julie Perron, professionnelle de recherche de l'équipe, de même que les étudiantes faisant partie de l'équipe du Dre Robitaille pendant mon doctorat, soit Mélissa Bélanger, Roxanne Mercier et Michèle Kearney, ont grandement contribué au recrutement des participants et à la collecte de données. Les chercheurs impliqués dans ce grand projet, en plus du Dre Robitaille, sont S. John Weisnagel, André Tchernof et Isabelle Marc. Les résultats de mes travaux découlant du projet GDM2 ont été publiés ou accepté pour publication dans 4 journaux scientifiques à la suite d'une révision par les pairs. Tous les coauteurs ont révisé ces manuscrits.

Chapitre 5: Dugas C, Kearney M, Perron J, Weisnagel SJ, Marc I, Robitaille J. Breastfeeding and growth trajectory from birth to 5 years among children exposed and unexposed to gestational diabetes mellitus in utero. *Journal of Perinatology*. May 2021;41(5):1033-1042.

Chapitre 7: Dugas C, Perron J, Marc I, Weisnagel SJ, Robitaille J. Association between early introduction of fruit juice during infancy and childhood consumption of sweet-tasting foods and beverages among children exposed and unexposed to gestational diabetes mellitus in utero. *Appetite*. Jan 1 2019;132:190-195.

Chapitre 8 : Dugas C, Bélanger M, Perron J, Weisnagel S.J, Tchernof A, Marc I, Robitaille J. Is A Healthy Diet Associated with Lower Anthropometric and Glycemic Alterations in

Predisposed Children Born from Mothers with Gestational Diabetes Mellitus? *Nutrients*. Mar 7 2019;11(3).

Chapitre 9 : Dugas C, Brassard D, Bélanger M, Perron J, Weisnagel S.J, Marc I, Robitaille J. Determinants of Healthy Diet among Children Exposed and Unexposed to Gestational Diabetes. *Journal of Nutrition Education and Behavior*. Accepté pour publication le 13 novembre 2021.

Dans le cadre du projet DÉPART, des femmes ayant eu une grossesse compliquée par un DG ont été recrutées deux mois après l'accouchement pour un projet d'intervention de 18 mois. J'ai collaboré à l'élaboration du matériel utilisé pour réaliser l'enseignement nutritionnel auprès des femmes de cette étude avec Dre Julie Robitaille (principale chercheuse du projet), Julie Perron (professionnelle de recherche) ainsi que les étudiantes à la maitrise de l'équipe pendant cette période (Michèle Kearney, Roxanne Mercier et Mélissa Bélanger). J'ai été la nutritionniste principale sur ce projet, ce qui impliquait la rencontre des participantes des groupes intervention et contrôle pendant la durée de l'intervention de 18 mois. Le lait maternel recueilli lors des rencontres a été utilisé pour réaliser les travaux présentés au chapitre 6 de cette thèse. Les chercheurs impliqués dans l'élaboration du projet DÉPART sont Isabelle Marc, S. John Weisnagel, André Tchernof, Catherine Bégin, Sophie Desroches et Stéphanie May Ruchat, en plus de Julie Robitaille. Des femmes sans antécédent de DG ont aussi été recrutées afin d'ajouter un groupe contrôle aux résultats du chapitre 6. Ces femmes ont participé à une seule rencontre, deux mois après l'accouchement, pendant laquelle elles étaient soumises aux mêmes tests et questionnaires que les femmes du projet DÉPART lors de leur première visite pour le projet DÉPART, et du lait maternel a été collecté. J'ai contribué à l'élaboration de ce projet pilote en collaboration avec les chercheurs impliqués dans ce projet (Julie Robitaille, Alain Veilleux, Alain Doyen et Vincenzo di Marzo). J'ai réalisé le recrutement et les rencontres de participantes avec Julie Perron, professionnelle de recherche de l'équipe. Les analyses de la composition du lait maternel ont été réalisées par Nadine Leblanc, Gabrielle St-Arnaud, Véronique Perreault et Véronique Richard. J'ai par la suite analysé et interprété les données recueillies et rédigé l'article scientifique. Finalement, Laurence Laberee a contribué à l'interprétation des données présentées dans l'article lors d'un stage d'été en recherche au sein de notre équipe. Tous les coauteurs ont révisé l'article scientifique présenté au chapitre 6.

Chapitre 6 : Dugas C, Laberee L, Perron J, St-Arnaud G, Richard V, Perreault V, Leblanc N, Marc I, Di Marzo V, Doyen A, Veilleux A, Robitaille J. Association between gestational diabetes mellitus, macronutrients content of human milk and infant growth. Article en révision au *British Journal of Nutrition*, soumis le 9 octobre 2021.

Introduction générale

L'obésité infantile est un problème préoccupant et est associé à différentes complications cardiométaboliques pouvant mener à des maladies chroniques plus tard dans la vie.[1] Certaines études suggèrent que le nombre d'années vécues en surplus pondéral serait fortement associé au risque de mortalité de toutes causes ainsi qu'au risque de mortalité due à des maladies cardiovasculaires.[2] Ainsi, il devient primordial d'établir des stratégies d'intervention tôt dans la vie d'un individu à risque d'obésité afin d'en prévenir son développement et les complications qui en découlent.

Bien que l'état de santé d'un individu puisse être en partie déterminé par sa génétique et son mode de vie, de plus en plus d'études s'intéressent au rôle de l'environnement au début de la vie de l'enfant dans le développement de sa santé à plus long terme.[3] Plus précisément, on reconnait maintenant les 1000 premiers jours de vie, c'est-à-dire la période allant de la conception jusqu'à l'âge de deux ans, comme étant une période critique du développement de l'enfant.[3, 4] Plusieurs facteurs environnementaux dans cette période sont susceptibles d'affecter le développement à plus long terme, dont l'alimentation.[4] En effet, de nombreuses études suggèrent que l'allaitement maternel pourrait aider à prévenir l'obésité chez l'enfant allaité, en partie dû à la composition unique du lait maternel.[5] L'introduction de différents aliments en complément au lait maternel ou aux préparations commerciales pour nourrissons pourrait aussi jouer un rôle dans le développement de la santé de l'enfant ainsi que dans le développement de ses préférences alimentaires.[6, 7] L'adoption de saines habitudes alimentaires en bas âge serait d'ailleurs une stratégie intéressante dans la lutte à l'obésité puisque plusieurs études ont démontré que les habitudes de vie acquises tôt dans la vie sont généralement maintenues pendant l'enfance et l'adolescence.[8]

Parmi les enfants à risque de développer de l'obésité, ceux ayant été exposés au DG pendant la grossesse présentent un risque de 1,45 à 2,80 fois supérieur aux enfants nés de grossesses en santé.[9, 10] Ces enfants sont aussi plus à risque de développer le DT2 plus tard la vie.[11] À ce jour, peu de stratégies ont été établies au sein de cette population afin de prévenir les complications à long terme associées à une exposition intra-utérine au DG.[12] Dans le cadre de mon doctorat, le rôle de l'alimentation, de la naissance à l'enfance, dans la prévention des complications associées à une exposition intra-utérine au DG a été investigué. Plus précisément, les résultats présentés dans cette thèse sont divisés en 6 chapitres suivant un ordre chronologique selon les étapes de la vie alimentaire de l'enfant, passant de l'allaitement maternel à l'introduction des aliments, pour terminer avec l'alimentation pendant l'enfance. Le chapitre 4, premier chapitre des résultats, présente les résultats d'une revue systématique de la littérature portant sur l'association entre l'allaitement maternel et le risque d'obésité chez des enfants ayant été exposés au DG *in utero*, permettant ainsi de situer l'état des connaissances sur le sujet. Ensuite, le chapitre 5 porte sur l'association entre l'allaitement maternel et la croissance de 0 à 5 ans des enfants exposés ou non-exposés au DG. Le 6^{e} chapitre porte quant à lui sur l'association entre le DG, la composition du lait maternel en macronutriments et la croissance de ces enfants. Le chapitre 7 met en relation le moment d'introduction des jus de fruits chez le nourrisson et la consommation d'aliments et boissons au goût sucré pendant l'enfance, toujours chez des enfants exposés ou non-exposés au DG. Finalement, les chapitres 8 et 9 portent sur l'association entre une saine alimentation et la santé cardiométabolique des enfants exposés ou non-exposés au DG *in utero* ainsi que sur les déterminants individuels et environnementaux de la qualité de l'alimentation des enfants, respectivement.

Chapitre 1 Programmation de la santé : la période prénatale

1.1 Origine développementale de la santé et des maladies

Le concept de programmation de la santé a été proposé pour la première fois dans les années 1970 par Günter Dörner pour expliquer le phénomène par lequel certaines composantes présentes dans des périodes critiques du développement fœtal, comme des hormones ou des métabolites, pourraient influencer la santé à long terme.[13] Ce concept a par la suite été popularisé par les travaux de David Barker qui, dans les années 1980, s'est intéressé au lien entre les conditions de vie des individus nés dans les années 1920-1925 dans certaines régions de l'Angleterre et du pays de Galles et le haut taux de mortalité infantile, ainsi que le haut taux de maladies coronariennes dans les années 1970 dans ces mêmes régions.[14] Barker a ainsi proposé une théorie selon laquelle les conditions de vie défavorables chez la femme enceinte auraient des impacts sur le bébé à naître et ce, jusqu'à l'âge adulte. [14, 15] Supportant cette théorie, d'autres travaux du même auteur ont démontré une association entre un faible poids à la naissance et un risque accru de mourir d'une maladie coronarienne plus tard dans la vie.[16] David Barker a aussi collaboré à la célèbre *Dutch Famine Birth Cohort Study*, une étude effectuée chez les enfants nés de grossesses ayant eu lieu pendant la famine engendrée par la deuxième guerre mondiale.[17] Les résultats de cette étude de cohorte ont démontré qu'un état de sous-alimentation pendant la grossesse était associé à une plus faible croissance fœtale et augmentait le risque de développer une intolérance au glucose et des maladies coronariennes plus tard dans la vie.[17]

1.1.1 Le phénotype d'épargne

Le mécanisme proposé par Barker et Hales pour soutenir les résultats des travaux présentés plus haut est celui du phénotype d'épargne, ou *thrifty phenotype* en anglais, qui suggère que le fœtus doive s'adapter aux conditions intra-utérines lors d'une sous-alimentation maternelle pour assurer sa survie, et que ces adaptations seraient permanentes, affectant ainsi la santé à long terme de l'enfant.[18] Par exemple, ils proposent qu'une malnutrition pendant la grossesse pourrait altérer la fonction pancréatique, en affectant le développement des cellules bêta du pancréas dans un moment critique de leur développement, ce qui expliquerait le risque accru d'intolérance au glucose plus tard dans la vie chez les individus exposés *in utero* à la famine.[18, 19] Cette hypothèse est supportée par des modèles animaux démontrant qu'un apport insuffisant en protéines pendant la grossesse entrainerait une réduction de la masse des cellules bêta du pancréas chez la descendance.[20]

Les études précédentes sont basées sur des situations de privation alimentaire et permettent d'expliquer l'augmentation du risque de certaines maladies, comme l'obésité et le DT2, au sein de populations vulnérables. Bien que l'hypothèse de Barker ciblât initialement la malnutrition pendant la grossesse, il est possible d'élargir le concept d'origine développementale de la santé et des maladies (en anglais, *Developmental Origin of Health and Diseases*) à toutes conditions affectant l'environnement intra-utérin auquel le fœtus devra s'adapter pour y survivre, y compris un environnement riche en nutriments.

1.2 La suralimentation pendant la grossesse

La recherche entourant le rôle d'une suralimentation pendant la grossesse sur le risque de surplus de poids ou d'obésité chez les bébés a suscité de l'intérêt dès le début des années 1930, à la suite d'observations cliniques démontrant que les bébés de femmes atteintes de diabète avaient un poids plus élevé à la naissance.[21] À la suite de ces observations, il a été suggéré qu'un environnement riche en nutriments, comme dans le cas d'un diabète non-contrôlé où les niveaux de glucose sont élevés, fournirait au fœtus une grande quantité de nutriments et entrainerait une augmentation de sa croissance intra-utérine.[21] Pour compléter cette théorie, Pedersen a proposé que le fait d'être exposé à des hauts niveaux de glucose entrainerait une hyperglycémie réactionnelle chez le fœtus, ce qui amènerait ce dernier à sécréter davantage d'insuline.[22] L'exposition à des niveaux élevés de cette hormone entrainerait donc une augmentation de la croissance fœtale, augmentant ainsi son risque de macrosomie et d'obésité plus tard dans la vie.[22]

Plusieurs études réalisées au sein de populations où la prévalence de l'obésité et du DT2 est élevée, comme chez les Indiens Pimas aux États-Unis, ont permis d'étudier le rôle d'un environnement riche en nutriments pendant la grossesse sur la croissance de l'enfant.[21] Les Indiens Pimas vivent dans le désert de l'Arizona depuis près de 2 000 ans.[23] L'arrivée des colons à la fin du XIX^{ème} siècle a entrainé une modification de leurs habitudes de vie, puisque ces derniers se sont appropriés leurs terres, les obligeant à passer du travail d'agriculteur à un mode de vie sédentaire ainsi qu'à consommer des aliments transformés plutôt que leurs récoltes d'aliments.[23] À la suite de ce changement drastique d'habitudes de vie, une augmentation marquée de la prévalence d'obésité et de DT2 a été observée dans cette population.[23] Au début des années 2000, plus de la moitié des adultes de 35 ans et plus dans cette population étaient atteints de DT2, alors que la prévalence de l'obésité s'élevait à 64% chez les hommes et 73% chez les femmes de 25 à 44 ans.[23]

Bien que cette situation soit déplorable, elle a permis la réalisation de plusieurs études très pertinentes permettant de mieux comprendre les liens entre différents paramètres de l'environnement et la santé. Notamment, une étude réalisée au sein de cette population a permis de déterminer que le risque de DT2 était 3,7 fois supérieur chez les enfants nés de mères ayant développé un DT2 avant leur grossesse, comparativement à leur frère ou leur sœur nés avant le diagnostic de diabète de leur mère.[24] Dans cette même étude, l'indice de masse corporelle (IMC) des enfants nés de mère diabétiques était plus élevé de 2,6 unités comparativement à leurs frères ou sœurs nés de la même mère avant le diagnostic de diabète de celle-ci.[24] Le schéma de cette étude permet donc de conclure que le risque élevé d'obésité et de DT2 chez les enfants ayant été exposés *in utero* au diabète n'est pas seulement le résultat d'une prédisposition génétique ou d'un partage d'environnement obésogène avec leur mère, mais que l'environnement intra-utérin entrainerait bel et bien des modifications chez les fœtus qui ont des impacts à plus long terme sur sa santé.[21] D'ailleurs, aucune association entre la présence d'un diabète paternel au moment de la grossesse et la prévalence de DT2 ou l'IMC des enfants n'a été établit dans cette étude, soutenant aussi le rôle de l'environnement intra-utérin sur la santé de l'enfant.[24]

Une étude réalisée en Suède où la prévalence de l'obésité et du diabète est moins grande que chez les Indiens Pimas a permis d'obtenir des résultats similaires.[25] En effet, dans cette cohorte composée de 280 866 hommes, dont plus de 81 000 avaient un frère inclus dans l'étude, l'IMC des hommes ayant été exposés au diabète pendant la grossesse était supérieur de 0,89 unités à l'âge de 18 ans comparativement à leur frère plus âgé et né avant le diagnostic de diabète de leur mère.[25]

Ainsi, la recherche actuelle s'intéresse davantage à l'impact de l'obésité maternelle ou du diabète lors de la grossesse sur la santé de l'enfant, considérant que ces deux problématiques de santé sont en croissance continue dans les pays industrialisés.[26] Le DG représente donc un modèle de suralimentation pendant la grossesse et sera étudié dans cette thèse de doctorat.

1.3 Le diabète gestationnel

1.3.1 Définition

Le DG se définit comme une hyperglycémie qui survient ou qui est diagnostiquée pour la première fois lors de la grossesse.[27] Des adaptations physiologiques se produisent chez la femme enceinte afin de permettre au fœtus de combler ses besoins en nutriments.[11] Notamment, à partir du 2e trimestre de la grossesse, la sensibilité à l'insuline chez la femme enceinte est diminuée, certains auteurs ayant estimé cette diminution à plus de 60% de son seuil habituel. [28, 29] Cette résistance à l'insuline survient à la suite d'une augmentation de la sécrétion de différentes hormones placentaires antagonistes à l'insuline, comme la progestérone et l'estrogène, de même qu'à la suite d'une augmentation du tissu adipeux de la femme au courant de la grossesse. [11, 30] En réponse à cette résistance à l'insuline, un état d'hyperinsulinisme réactionnel s'installe chez la femme enceinte, le pancréas produisant alors des niveaux d'insuline jusqu'à 30% supérieur lors du 3e trimestre comparativement aux niveaux prégravide.[31] Des études chez l'animal suggèrent que cette augmentation de l'insuline serait le résultat d'une hyperplasie et d'une hypertrophie des cellules bêta du pancréas.[32] Cependant, chez certaines femmes, le pancréas ne parviendrait pas à produire suffisamment d'insuline pour contrer cet état de résistance à l'insuline induit par la grossesse, résultant en des niveaux plasmatiques de glucose élevés et menant au diagnostic de DG[11].

Dans certains cas, l'hyperglycémie se produirait seulement pendant la grossesse et la glycémie retrouverait des valeurs normales après l'expulsion du placenta lors de l'accouchement.[11] Cependant, dans près de 80% des cas, la grossesse représenterait un moment clé pour identifier une altération des cellules bêta du pancréas dû à une résistance à l'insuline chronique, qui serait exacerbée pendant la grossesse et qui aurait tendance à se détériorer avec le temps.[11, 33] Cela expliquerait donc en partie le risque 10 fois plus élevé de développer un DT2 dans les années suivant une grossesse compliquée par un DG.[34] C'est pour cette raison que Diabète Canada recommande d'effectuer un test de dépistage du diabète dans les six semaines à six mois suivant l'accouchement chez les femmes ayant eu un DG.[35]

1.3.2 Critères diagnostiques

Il existe différents critères diagnostiques du DG selon les pays et régions du monde.[36] Les critères diagnostiques utilisés par Diabète Canada comportent deux approches, l'une privilégiée et la seconde considérée comme une approche alternative.[37] La première approche consiste en un diagnostic réalisé en deux étapes, débutant par un test d'hyperglycémie provoquée par voie orale (HGPO) avec une dose de 50g de glucose effectué entre la 24[e] et 28[e] semaine de la grossesse. Un diagnostic de DG sera directement établi si la glycémie excède 11.0 mmol/L au premier test. Cependant, lorsque la valeur de la glycémie se retrouve entre 7,8 et 11,0 mmol/L une heure après l'ingestion de la charge de glucose, la femme doit reconduire un second test d'HGPO cette fois-ci avec 75g de glucose. Pour les femmes devant reconduire un test d'HGPO de 75g, le diagnostic de DG est établi lorsque l'une des trois valeurs suivantes est atteinte: glycémie à jeun ≥ 5,3 mmol/L, glycémie 1h post HGPO ≥ 10,6 mmol/L ou glycémie 2h post HGPO ≥ 9,0 mmol/L (**Figure 1. 1**).

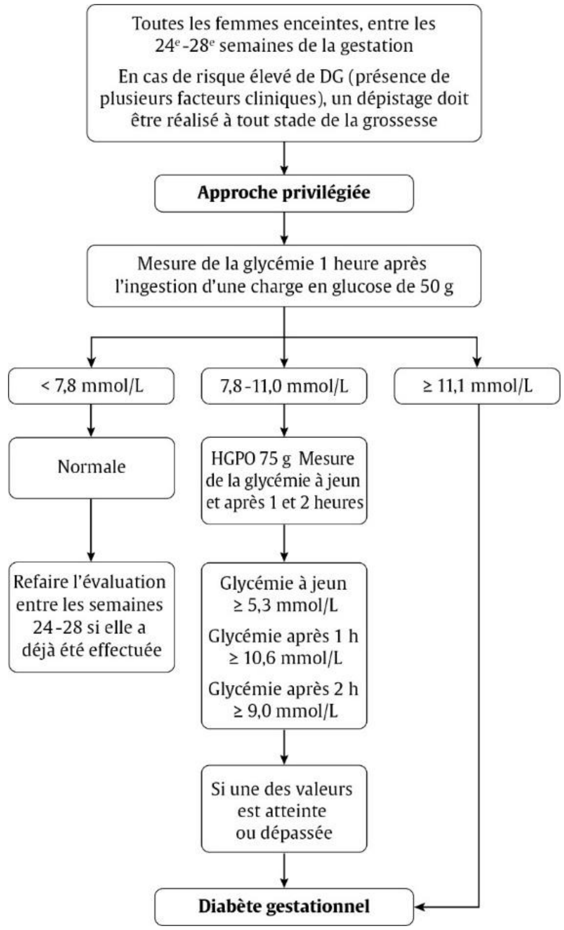

Figure 1. 1 Approche privilégiée de Diabète Canada pour le diagnostic de diabète gestationnel [37]

L'approche alternative utilisée par Diabète Canada (**Figure 1. 2**) pour établir le diagnostic de DG est celle de *l'International Association of Diabetes and Pregnancy Study Groups* (IADPSG) qui a été établi en 2008 à la suite d'un congrès international sur le DG.[37, 38] Le but de cette convention était d'établir un consensus concernant de nouvelles lignes directrices pour le diagnostic du DG basées sur les effets de l'hyperglycémie maternelle sur la santé de l'enfant, contrairement aux lignes directrices datant de plusieurs décennies et toujours utilisées à l'époque qui se basaient plutôt sur le risque maternel de développer le DT2 après la grossesse [38]. Ainsi, les résultats de l'étude *Hyperglycemia and Adverse Prengancy Outcomes* (HAPO) ont été utilisés pour établir ces nouveaux critères diagnostiques.[39] L'étude HAPO, incluant environ 25 000 participantes provenant de 15 centres de recherche de 9 pays différents, avait pour objectif d'étudier l'effet de la glycémie maternelle sur différents paramètres obstétricaux et périnataux.[39] Les résultats de cette étude ont permis de démontrer que la glycémie maternelle était associée de façon positive et continue à différentes complications de la grossesse, dont un risque accru de donner naissance à un bébé de poids élevé.[39] Ces résultats ont donc mis en lumière la nécessité de réviser les critères diagnostiques utilisés à cette époque, résultant en des critères plus sévères et ciblant davantage de femmes. Ces critères sont maintenant adoptés par différents regroupements, dont Diabète Canada (approche alternative) et l'Organisation mondiale de la santé (OMS).[37, 40] Cependant, ils demeurent controversés puisque certains chercheurs soulignent le fait que les bénéfices associés au traitement d'un si grand nombre de femmes n'ont pas été démontrés dans le cadre d'un essai randomisé contrôlé.[41]

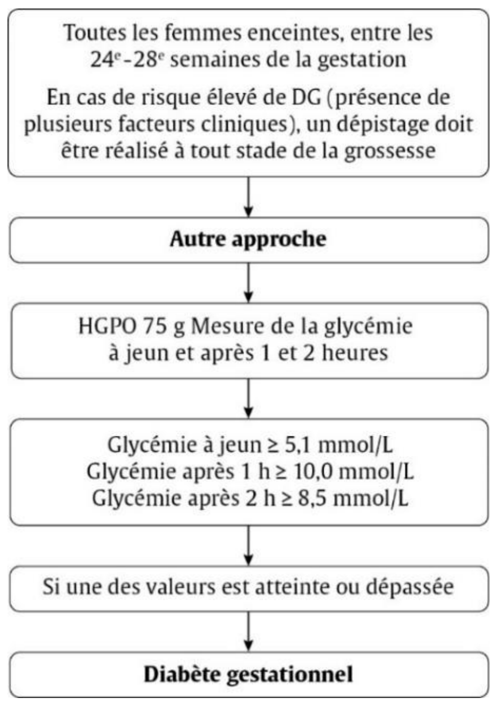

Figure 1. 2 Critères du diagnostic de diabète gestationnel selon l'International Association of Diabetes and Pregnancy Study Groups

1.3.3 Prévalence

Considérant la multitude de critères diagnostiques du DG utilisés, il devient difficile d'établir une prévalence mondiale de cette pathologie.[36] Malgré tout, de tels chiffres existent, entre autres ceux de la Fédération internationale du diabète (FID) qui, en 2019, a établi qu'une naissance sur six serait issue d'une grossesse compliquée par un DG.[42, 43] La FID utilise les données de 51 études de 41 pays différents pour estimer la prévalence du DG par pays. Ainsi, au Canada, la prévalence du DG s'élèverait à 14,6% selon ces données.[43] Au Québec, selon les données de l'Institut nationale de santé publique du Québec (INSPQ), la prévalence du DG aurait triplée entre 1989 et 2012, passant de 2,5 à 7,6% des grossesses en deux décennies (**Figure 1. 3**).[44]

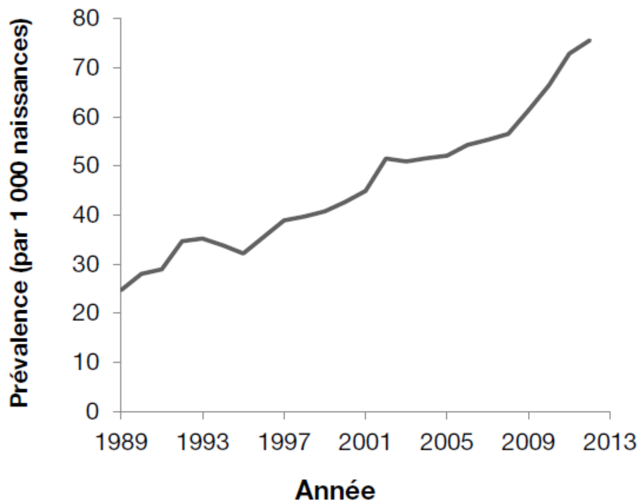

Figure 1. 3 Prévalence du diabète gestationnel au Québec[44]

Plusieurs facteurs peuvent expliquer l'augmentation de la prévalence du DG au Québec et à travers le monde, notamment l'introduction des nouveaux critères diagnostiques établis par l'IADPSG. En effet, l'utilisation de ces critères a entrainé une augmentation de la prévalence du DG de deux à cinq fois supérieures chez certaines populations comparativement à la prévalence décelée par des critères locaux, puisqu'ils sont plus sévères et davantage de femmes sont diagnostiquées positivement.[36, 45, 46] Il a aussi été suggéré que l'augmentation de la prévalence du DG pourrait être une conséquence de l'augmentation du DT2 dans les pays développés, dû à la sédentarisation et aux environnements non favorables à l'adoption de saines habitudes de vie.[36, 47] Ainsi, certaines femmes pourraient avoir un diabète préexistant à la grossesse non diagnostiqué, qui serait alors décelé pour la première fois lors de l'HGPO pendant la grossesse. D'un autre côté, on ne peut exclure le fait que le DG entrainerait lui-même une augmentation des cas de DT2 dans la population et serait alors un facteur contributeur à l'épidémie de DT2 que connait les pays occidentaux.[34]

Finalement, les variations de prévalence du DG à travers le monde peuvent aussi s'expliquer par la présence de différents facteurs de risque selon les différentes populations.[36] En effet, les facteurs de risque du DG incluent l'origine ethnique (populations asiatiques et hispaniques), l'âge avancé lors de la grossesse, un IMC pré grossesse élevé, un gain de poids gestationnel excessif, une alimentation de moins bonne qualité, l'exposition intra-utérine au diabète, une histoire familiale de diabète ou encore d'autres pathologies associées à une résistance à l'insuline, comme le syndrome des ovaires polykystiques.[11, 48, 49]

1.3.4 Complications chez l'enfant

Néonatales

Tel que discuté précédemment, le DG représente un modèle de suralimentation pendant la grossesse et est associé à une croissance fœtale accrue suivant les principes de l'hypothèse de Pedersen.[22, 50] Dans ce contexte, l'augmentation de dépôt de masse adipeuse chez le fœtus augmente son risque de macrosomie à la naissance.[51] La macrosomie, définie comme un poids de naissance de plus de 4000g ou supérieur au 90^{e} percentile, est en effet trois fois plus fréquente chez les enfants ayant été exposés au DG comparativement aux enfants nés de grossesses en santé.[51] Cette condition est associée à un risque de différentes complications néonatales comme l'accouchement prématuré, la naissance par césarienne ou encore la dystocie des épaules chez le nouveau-né.[51, 52] Elle est aussi associée à un risque accru de surplus de poids ou d'obésité plus tard dans la vie.[53]

Surplus de poids ou obésité

Plusieurs études ont démontré une association positive entre une exposition intra-utérine au DG et la prévalence de surplus de poids ou d'obésité plus tard dans la vie.[10, 54] Une étude réalisée dans notre équipe de recherche a de plus démontré que les mesures adipeuses des enfants ayant été exposé au DG *in utero*, incluant le tour de taille et la masse grasse androïde, étaient supérieures à celles des enfants du groupe contrôle et ce, malgré un IMC similaire entre les deux groupes.[55] Ces enfants étaient âgés en moyenne de six ans, ce qui suggère que des altérations métaboliques apparaitraient assez tôt dans la vie de l'enfant exposé *in utero* au DG[55], mais que le risque de surplus de poids ou d'obésité mesuré avec l'IMC pourrait être décelé seulement plus tard pendant l'adolescence ou à l'âge adulte.

Bien que certaines études suggèrent que l'obésité maternelle pourrait être un médiateur de l'association entre l'exposition au DG et l'obésité chez l'enfant[56], plusieurs études soutiennent que le DG représenterait plutôt un facteur de risque indépendant de l'obésité chez l'enfant exposé *in utero*.[54] Notamment, les résultats du suivi pendant l'enfance de l'étude HAPO ont permis de déterminer que la glycémie maternelle, à des valeurs inférieures à celles correspondant au diagnostic de DG, était corrélée de façon positive et linéaire aux valeurs d'adiposité chez l'enfant à l'âge de 10 à 14 ans et ce, indépendamment de l'IMC de la mère.[57] D'autres auteurs ont aussi démontré une association entre l'exposition intra-utérine au diabète et le risque de surplus de poids ou d'obésité chez l'enfant qui demeurait significative après avoir ajusté les analyses pour l'IMC de la mère.[10, 25, 58] De plus, le poids à la naissance élevé ne serait pas le seul facteur contribuant au risque de surplus de poids ou d'obésité chez ces enfants puisque certaines études démontrent des associations qui demeurent significatives après avoir pris en considérant le poids à la naissance de l'enfant.[59]

Intolérance au glucose et diabète de type 2

Plusieurs études ont démontré que les enfants ayant été exposés au DG *in utero* présenteraient un risque accru d'intolérance au glucose ou de DT2 plus tard dans la vie.[54, 60-62] Le risque accru de DT2 observé chez ces enfants serait en partie dû à une altération permanente de la fonction pancréatique ou de la sensibilité à l'insuline causée par l'exposition à un milieu intra-utérin riche en glucose.[63] En effet, selon une étude menée chez des enfants de 5 à 10 ans nés de femmes avec un DG, l'hyperglycémie maternelle serait inversement associée à la sensibilité à l'insuline et positivement à la réponse des cellules bêta du pancréas chez l'enfant et ce, indépendamment de son adiposité.[63] De plus, les résultats de l'étude de suivi de la cohorte HAPO ont démontré que les enfants exposés au DG *in utero* présentaient un état de résistance à l'insuline, mais une réponse limitée des cellules bêta du pancréas à l'âge de 10 à 14 ans comparativement aux enfants non-exposés au DG.[64] Des études *in vitro* et chez l'animal ont d'ailleurs confirmé cette hypothèse en démontrant une altération dans le développement des cellules bêta du pancréas, une altération de la sécrétion d'insuline et une réduction de la sensibilité à l'insuline à la suite d'une exposition à un environnement riche en glucose.[65-67] Ainsi, les enfants ayant été exposés au diabète *in utero* présenteraient un état d'hyperinsulinisme en bas âge, qui serait suivi d'un déclin de la sécrétion de cette hormone avec l'âge.[68] Ces études suggèrent donc que l'hyperglycémie maternelle influencerait directement le risque d'intolérance au glucose ou de DT2 chez l'enfant via des mécanismes de programmation fœtale.

Une étude réalisée chez les Indiens Pimas a d'ailleurs démontré que les enfants nés après le diagnostic de diabète de leur mère avaient un risque augmenté de développer le DT2 de 3,7 fois supérieur à ceux des enfants nés avant le diagnostic de diabète de leur mère.[24] L'augmentation de la prévalence du DT2 pendant l'enfance chez les Indiens Pimas a d'ailleurs été attribuée en partie à l'augmentation de la prévalence du diabète pendant la grossesse chez les femmes en âge de procréer.[69]

1.3.5 Prévention des complications en période prénatale

Tout d'abord, la prévention du DG chez les femmes en âge de procréer est essentielle afin de diminuer les impacts du DG sur sa santé et celle de son enfant. Parmi les stratégies de prévention, l'adoption de saines habitudes de vie, y compris l'adoption d'une saine alimentation et la pratique d'activité physique, pourrait permettre de prévenir le développement du DG chez la femme enceinte.[70, 71] De plus, le suivi des recommandations concernant le gain de poids gestationnel pourrait aussi permettre de prévenir le développement du DG. [72] En effet, il a été démontré qu'un gain de poids gestationnel excessif en début de grossesse augmenterait le risque de développer un DG lors de cette grossesse [48, 73].

Par la suite, lorsque le DG est diagnostiqué, un contrôle glycémique adéquat de la femme enceinte a été démontré comme étant efficace pour réduire le risque de macrosomie chez le nouveau-né.[74] Cependant, certaines études ont démontré que même si le traitement du DG permettait de réduire significativement le risque d'avoir un bébé de poids élevé à la naissance, il ne permettait pas de prévenir le risque d'avoir un IMC plus élevé pendant l'enfance.[75, 76]

Ces résultats soulignent donc l’importance d’établir d’autres stratégies d’intervention chez cette population afin de prévenir l’apparition de complications de santé à l’âge adulte et ultimement, de rompre la transmission intergénérationnelle de l’obésité et du diabète chez la descendance.

Chapitre 2 Programmation de la santé : la période postnatale

2.1 Les 1000 premiers jours de vie

Contrairement à ce que semble suggérer l'hypothèse de Barker, la plasticité du développement de la santé n'est pas contrainte à la période fœtale. En effet, le développement des différents systèmes de l'être humain se produit en grande partie pendant ses 1000 premiers jours de vie, ce qui inclut la période de la conception jusqu'à la fin de la deuxième année de vie de l'enfant.[77] Ainsi, plusieurs facteurs sont susceptibles d'influencer le développement dans cette période critique du développement, ce qui aura un impact sur la santé de l'individu à plus long terme.[77] Parmi ces facteurs, l'alimentation en début de vie de l'enfant jouerait un rôle clé dans ces mécanismes de programmation.[4] D'ailleurs, dans un rapport de la *British Medical Association* paru en 2009, l'alimentation pendant la grossesse et le début de vie de l'enfant a été reconnue comme étant critique pour le développement à long terme de celui-ci, avec de nombreuses évidences suggérant une association entre l'alimentation dans ces périodes et le développement de maladies coronariennes et du DT2 plus tard dans la vie.[78] Le Fonds des Nations Unies pour l'enfance (UNICEF) reconnait aussi que l'alimentation dans les 1000 premiers jours de vie contribue à l'établissement de la santé de l'individu à plus long terme, tant dans les pays en développement où la sous-alimentation peut affecter le développement de l'enfant que dans les pays industrialisés où la suralimentation dans cette période critique aurait aussi des effets néfastes à long terme.[79]

2.2 L'allaitement maternel

L'alimentation dans les six premiers mois de vie est principalement composée de lait maternel et/ou des préparations commerciales pour nourrissons. Dû à ses nombreux effets bénéfiques sur la santé de l'enfant, l'allaitement maternel est d'ailleurs recommandé par l'OMS de façon exclusive pour les six premiers mois de vie de l'enfant, suivi par un allaitement complémentaire aux aliments jusqu'à l'âge de deux ans.[80] Cette recommandation est la même dans plusieurs pays du monde, dont le Canada.[81]

2.2.1 Prévalence de l'allaitement maternel

Population générale

Au Canada, l'initiation de l'allaitement maternel est passé de 25% en 1965 à 90% dans les années 2015-2016, ce qui représente une augmentation très importante de cette pratique au pays.[82] Cette augmentation peut s'expliquer par une plus grande promotion de l'allaitement au fil des années ainsi que par l'implantation des politiques de l'Initiative hôpitaux amis des bébés (IHAB) dans nos établissements de santé.[83] L'IHAB est une stratégie mondiale lancée en 1991 par l'OMS et l'UNICEF afin d'établir des stratégies de succès pour l'allaitement maternel dans les établissements de santé.[83] Plusieurs études ont d'ailleurs démontré l'efficacité de ce programme sur l'amélioration de l'initiation et de la durée de l'allaitement maternel. [84-86] Cependant, malgré cette forte augmentation de l'initiation de l'allaitement au pays dans le dernier siècle, la prévalence des femmes atteignant la recommandation de l'OMS concernant la durée de l'allaitement exclusif demeure faible. En effet, selon les données de l'Enquête sur la santé dans les collectivités canadiennes (ESCC) de 2011-2012, la proportion des femmes ayant allaité exclusivement leur enfant pendant les six premiers mois de vie était de 26% au Canada.[87] Au Québec, cette proportion était plutôt de 19% pour ces mêmes années.[87] Différentes raisons ont été évoquées par les mères pour expliquer l'arrêt de l'allaitement maternel, comme une production de lait insuffisante pour répondre aux besoins du bébé ou encore le fait d'avoir de la difficulté avec les différentes techniques d'allaitement.[87]

Diabète gestationnel

Plusieurs études ont démontré que les femmes ayant eu un DG auraient tendance à moins allaiter leur enfant de façon exclusive et pendant de moins longues périodes.[88, 89] Selon une revue systématique et méta-analyse conduite par Manerkar et collaborateurs, les enfants ayant été exposés au DG étaient 40% plus à risque de recevoir des préparations commerciales pour nourrissons à l'hôpital avant leur départ pour la maison, 30% moins susceptibles d'être allaités pendant plus de 12 mois et seraient allaités en moyenne un mois de moins que les enfants nés de mères sans DG.[88] Parmi les raisons pouvant expliquer ces résultats, il a été démontré que les femmes ayant eu un DG seraient plus à risque d'avoir un retard dans la phase d'activation sécrétoire (autrefois appelé la lactogénèse II).[90, 91] L'activation sécrétoire se produit quelques jours après la naissance et est le processus par lequel la glande mammaire produit du lait en grande quantité en réponse à certains changements hormonaux, notamment une diminution de la progestérone à la suite de l'expulsion du placenta jumelée à des niveaux élevés de prolactine.[92] Certaines évidences suggèrent que des niveaux plus faibles d'insuline chez les femmes atteintes de DG pourraient interférer avec les processus hormonaux impliqués dans l'activation sécrétoire, puisque l'insuline aurait un effet positif sur la production de prolactine, ce qui pourrait expliquer le délai observé dans la montée laiteuse de ces femmes.[93] En effet, selon une récente méta-analyse sur le sujet, le risque de retard dans la phase d'activation sécrétoire serait augmenté de 1,84 fois (IC 95% : 1,34–2,52) chez les femmes avec DG comparativement aux femmes sans DG, et cette problématique toucherait 35% des femmes avec DG.[90] Par la suite, les femmes ayant eu un retard dans la phase d'activation sécrétoire auraient tendance à allaiter sur une moins longue période et moins de façon exclusive.[94]

D'autres facteurs peuvent expliquer la durée d'allaitement plus courte chez les femmes ayant eu un DG. Par exemple, le fait que les bébés nés de femmes avec DG ont un risque plus élevé de complications néonatales, nécessitant parfois une admission aux unités de soins intensifs, peut entrainer un retard dans l'initiation de l'allaitement puisque les mères sont temporairement séparées de leur bébé.[95] Une étude américaine a aussi identifié différentes barrières à l'allaitement maternel chez des femmes avec et sans DG, ce qui a permis de constater que les femmes avec DG auraient un moins bon support social favorisant l'allaitement maternel (conjoint et/ou médecin qui préfèrent les préparations commerciales pour nourrissons à l'allaitement) et seraient moins à l'aise d'allaiter devant des amies.[96] De façon plus générale, un statut socioéconomique plus faible et un IMC plus élevé seraient associés à un plus faible taux d'allaitement à quatre et six mois, respectivement.[97] Ainsi, de l'éducation concernant les effets bénéfiques de l'allaitement maternel pour la santé de la femme et de son enfant, particulièrement dans des cas de DG, ainsi que le support offert à ces femmes devraient être accentués auprès de celles-ci.

2.2.2 Allaitement et obésité chez l'enfant

Population générale

Parmi les facteurs de risque prédisposant l'enfant au développement de l'obésité, le fait d'avoir été allaité ou non en bas âge représente un élément clé à considérer.[4] En effet, de nombreuses études ont permis d'établir une association entre l'allaitement maternel et la prévention de l'obésité chez les enfants dans la population générale.[98-100] Selon une récente méta-analyse incluant plus de 26 études prospectives, le risque d'obésité chez les enfants d'âge préscolaire ayant été allaités, comparativement à ceux non-allaités, était diminué de 17% (OR : 0,83, IC 95% : 0,73-0,94).[5] Cette relation serait d'ailleurs de nature dose-dépendante, où chaque mois additionnel d'allaitement serait associé à une réduction du risque d'obésité supplémentaire de 4%.[5, 101] L'allaitement exclusif, défini comme une alimentation composée uniquement de lait maternel sans autre solide ni liquide, serait aussi associé à une diminution du risque d'obésité de 47% comparativement aux enfant n'ayant jamais été allaités selon cette même méta-analyse (OR : 0,53, IC 95% 0,45 – 0,63).[5] Des résultats similaires ont été obtenus dans une étude de l'OMS conduite dans 22 pays d'Europe où le risque d'obésité à l'âge de 6-9 ans était supérieur chez les enfants non-allaités ou allaités moins de six mois, comparativement à ceux allaités pendant six mois ou plus (OR : 1,22, IC 95% 1,16–1,28 et 1,12, IC 95% 1,07–1,16, respectivement).[99] Ces analyses étaient ajustées pour l'âge et le sexe de l'enfant, le niveau d'éducation de la mère et son statut pondéral, le lieu de résidence, le poids à la naissance du bébé et son âge gestationnel à la naissance (bébé né à terme ou non).[99] À l'opposé, un des seuls essais randomisés et contrôlés évaluant l'effet d'une intervention visant la promotion de l'allaitement maternel n'a démontré aucune association significative entre la pratique de l'allaitement (augmentée grâce à l'intervention) et les mesures anthropométriques pendant l'enfance.[102] Cependant, force est de constater que la majorité des études sur le sujet démontrent plutôt une association négative entre l'allaitement maternel et les mesures de composition corporelle de l'enfant, y compris le risque de surplus de poids ou d'obésité. [103-105] Les résultats des différentes études conduites dans la population générale démontrent généralement un effet protecteur de l'allaitement et ce, du début de la vie de l'enfant jusqu'à l'âge adulte, ce qui suggère que l'allaitement maternel aurait des effets sur la santé à long terme d'un individu.[100]

Parmi les mécanismes pouvant expliquer l'association entre l'allaitement maternel et le risque diminué de surplus de poids ou d'obésité, la composition unique du lait maternel permettant la croissance optimale du bébé en serait un important. En effet, bien que les préparations commerciales pour nourrissons soient conçues pour imiter la composition du lait maternel, il est difficile de mimer ce fluide corporel. Il est adapté au nourrisson et sa composition fluctue selon son stade de développement ou encore selon les caractéristiques de la mère.[106] Par exemple, la quantité de protéines retrouvées dans le lait humain serait inférieure à celle retrouvée dans les préparations commerciales pour nourrissons.[107] En effet, comme les protéines bovines utilisées dans les préparations commerciales pour nourrissons sont moins bien absorbées et métabolisées par le nouveau-né que les protéines du lait humain, une quantité de protéines supérieure aux besoins de celui-ci doit être ajoutée aux préparations afin qu'il rencontre ses besoins en acides aminés essentiels.[108] Cependant, des apports excessifs en protéines en bas âge ont été associés à un IMC plus élevé pendant l'enfance, via une croissance accrue, ce qui pourrait donc expliquer le fait que les enfants nourris aux préparations commerciales ont un risque accru d'obésité plus tard dans la vie.[109] D'autres composantes bioactives présentes dans le lait maternel, comme des hormones associées à la régulation des apports alimentaires telles que la leptine et la ghréline, pourraient influencer la régulation de l'appétit de l'enfant allaité.[110, 111] Ainsi, un enfant allaité pourrait mieux réguler ses apports alimentaires, ce qui aiderait à diminuer son risque de surplus de poids ou d'obésité plus tard dans la vie, puisqu'il serait davantage à l'écoute de sa faim.[112] Dans le même ordre d'idées, des études ont démontré que les enfants nourris au biberon recevraient de plus grandes quantités de lait comparativement à ceux nourris au sein, possiblement dû au fait que les parents auraient tendance à vouloir offrir la totalité du contenu du biberon au bébé et ce, sans écouter les signaux de faim et de satiété de ce dernier.[113, 114] Finalement, certaines études ont aussi suggéré que l'allaitement maternel faciliterait l'acceptation des aliments au moment de leur introduction, ce qui serait associé à une meilleure qualité de l'alimentation chez l'enfant.[115] En effet, comme le lait maternel possède la propriété de changer de saveur selon les apports alimentaires de la mère, l'enfant allaité est exposé dès son plus jeune âge à différentes saveurs comparativement aux enfants nourris aux préparations commerciales pour nourrissons qui ne connaissent qu'une seule saveur d'aliment pendant les premiers mois de leur vie.[115-117] Cela se traduirait donc par une meilleure acceptation de nouveaux aliments, dont les légumes, ce qui en augmenterait leur consommation plus tard pendant l'enfance.[116, 117]

Diabète gestationnel

Plusieurs études se sont intéressées au lien entre l'allaitement maternel et la prévention de l'obésité chez les enfants ayant été exposés au diabète *in utero*, considérant que cette population présente un risque accru d'obésité.[88, 118, 119] Une revue narrative de la littérature réalisée dans le cadre de mon mémoire de maîtrise a permis de constater que la majorité des études conduites dans cette population démontraient une association négative entre l'allaitement maternel et le risque de surplus de poids ou d'obésité chez ces enfants, bien que certaines études présentaient également des résultats contradictoires.[118] Parmi les études ayant suscité le plus d'intérêt, celle réalisée par Plagemann et collaborateurs dans une population de femmes avec DG ou diabète de type 1 (DT1) a démontré que la consommation de lait maternel de femmes diabétiques dans les sept premiers jours de vie était associée à un IMC plus élevé à l'âge de deux ans, comparativement aux enfants exposés au diabète *in utero* qui recevaient plutôt du lait maternel de femmes sans diabète provenant d'une banque de lait maternel.[120] Ces résultats suggéraient donc un effet néfaste du lait maternel de femmes avec un diabète sur le poids de l'enfant. Cependant, dans une étude subséquente réalisée dans cette même cohorte, la consommation de lait maternel de femmes diabétiques dans les deux à quatre premières semaines de vie n'était pas associée à l'IMC à deux ans des enfants lorsque les analyses étaient ajustées pour la consommation de lait maternel dans les sept premiers jours de vie, suggérant l'importance des premiers moments de la vie de l'enfant dans la programmation de sa santé à plus long terme. [121] Bien qu'intéressante, cette étude inclut des femmes avec un diabète préexistant à la grossesse, ce qui pourrait influencer les résultats obtenus. En effet, les femmes avec un DT1 n'ont pas le même profil de santé que les femmes avec DG et sont généralement suivies par des professionnels de la santé dès le début de la grossesse[122], en plus d'avoir des pratiques d'allaitement et une composition du lait maternel différente des femmes avec DG.[123] Parmi les études réalisées chez les enfants ayant été exposés au DG uniquement, Aris et collaborateurs ont démontré que l'allaitement maternel pendant quatre mois ou plus était associé à un gain de poids et d'IMC plus grand pendant les six premiers mois de vie comparativement à une durée d'allaitement plus faible.[124]

Les résultats de la revue narrative publiée pendant ma maîtrise ont aussi permis de constater qu'une durée prolongée d'allaitement maternel semblait parfois nécessaire chez les enfants ayant été exposés au DG afin de voir une association négative entre l'allaitement et le risque de surplus de poids ou d'obésité plus tard dans la vie, comparativement aux enfants non-exposés au DG chez qui toute durée d'allaitement maternel semblait offrir un effet protecteur.[118] Par exemple, dans une étude conduite chez 2287 participants (dont 232 exposés au DG), toute durée d'allaitement maternel permettait d'observer une réduction du risque d'obésité de 66 à 79% chez les enfants du groupe contrôle, alors qu'une durée d'allaitement de 12 mois ou plus était nécessaire pour observer une diminution du risque d'obésité chez les enfants exposés au DG.[125] Ainsi, la majorité des études démontrent un effet bénéfique de l'allaitement maternel dans la prévention de l'obésité chez les enfants ayant été exposés au DG. Cependant, certains résultats demeurent contradictoires et plus d'études semblent nécessaires afin de mieux comprendre le rôle de l'allaitement maternel dans la prévention des complications associées à une exposition intra-utérine au DG, ainsi que les mécanismes expliquant ces associations.

2.2.3 La composition du lait maternel

Tel que mentionné plus haut, le lait maternel est l'aliment privilégié pour l'enfant pendant ses six premiers mois de vie. Il est difficile de déterminer la valeur nutritive exacte de ce fluide biologique puisque sa composition fluctue selon différents paramètres comme l'âge du bébé, le moment de la tétée, l'alimentation de la mère, sa composition corporelle, son âge ou encore l'état de santé de celle-ci au moment de l'allaitement.[126-130] Cependant, certaines généralités quant à la composition du lait humain ont été établies et permettent de mieux comprendre le rôle de l'allaitement sur la santé de l'enfant.

Population générale

Tout d'abord, la première phase de la lactogénèse se nomme la phase de différenciation sécrétoire (autrefois nommée la lactogénèse I) et représente la période pendant laquelle la glande mammaire se prépare à produire du lait.[131] Cette phase débute pendant la grossesse et se termine quelques jours après la naissance.[131] Le lait maternel sécrété lors de cette phase pendant les premiers jours de vie du bébé est appelé colostrum et possède une composition bien particulière.[106] En effet, le colostrum est très concentré en protéines, dont des protéines immunitaires comme l'immunoglobuline A, et est plutôt faible en lipides et en lactose.[106] Ce premier lait maternel est donc reconnu pour son rôle immunitaire sur la santé de l'enfant plutôt que pour son rôle nutritionnel.[106] Par la suite, lors de la phase d'activation sécrétoire (autrefois nommée la lactogénèse II), la glande mammaire produit du lait en plus grand volume et dont la composition change graduellement pour soutenir les besoins du bébé.[106] Le lait maternel dit « transitoire » correspond donc au lait produit entre les jours 5 et 14 de vie, approximativement, laissant place au lait dit « mature » par la suite. Le lait maternel est considéré comme étant complètement mature à partir des semaines quatre à six de vie suivant la naissance puisque sa composition sera beaucoup moins changeante à partir de ce moment que lors du premier mois de vie, bien que différents paramètres continueront d'influencer sa composition.[106]

Le contenu en lactose du lait maternel, le principal glucide retrouvé dans le lait humain, augmente graduellement du colostrum au lait mature pour atteindre des concentrations correspondant environ à 6,7 à 7,8 g/100 mL.[106] À l'inverse, la quantité de protéines dans le lait mature est beaucoup plus faible que dans le colostrum, avec des concentrations allant d'environ 0,9 à 1,2 g/100 mL dans le lait mature, cette proportion demeurant relativement stable par la suite.[106] La composition en lipides, quant à elle, est la composante la plus variable du lait maternel mature, autant au niveau inter-individuel qu'intra-individuel.[132] Par exemple, selon certaines études, la quantité de lipides du lait maternel serait plus importante dans le lait produit le jour comparativement à celui produit la nuit.[133] Le lait humain contiendrait aussi davantage de lipides à la fin d'une tétée comparativement au lait ingéré au début du boire, permettant ainsi un meilleur rassasiement à l'enfant désirant boire du lait pendant une plus longue période.[133] Au niveau interindividuel, certaines études ont démontré que la composition corporelle de la femme influencerait la quantité de lipides dans son lait, les femmes ayant un IMC plus élevé ayant davantage de lipides dans leur lait maternel.[134] L'alimentation serait aussi un déterminant de la quantité de lipides du lait.[135] En effet, selon une revue systématique publiée par Keikha et collaborateurs en 2017, plusieurs études observationnelles et d'intervention démontraient une association positive entre les apports en différents types d'acides gras et leur présence dans le lait maternel.[135] Ainsi, il est plus difficile d'estimer la quantité de lipides du lait mature. Certaines études ont démontré des valeurs variant de 22 à 62 g/L chez une même femme.[136]

Bien que l'intérêt pour l'étude de la composition du lait maternel ait débuté majoritairement dans les années 1960, de nouvelles composantes de ce fluide biologique ne cessent d'être découvertes encore aujourd'hui.[106] Aussi, de plus en plus de groupes de recherche s'intéressent aux facteurs pouvant influencer la composition du lait maternel ainsi que l'impact potentiel sur la santé de l'enfant allaité. En effet, tel que mentionné précédemment, la composition du lait maternel permettrait d'expliquer en grande partie les associations observées entre la pratique de l'allaitement et la prévention de différentes complications de santé, comme l'obésité.[110, 112]

Diabète gestationnel

Certaines études suggèrent que la composition du lait maternel serait altérée chez les femmes ayant eu un DG pendant la grossesse, ce qui expliquerait certains résultats contradictoires observés dans la littérature quant au rôle de l'allaitement maternel dans la prévention de l'obésité chez les enfants ayant été exposés au DG *in utero*.[137] En effet, une revue systématique publiée en 2020 par Peila et collaborateurs a permis d'identifier plusieurs composantes du lait maternel qui seraient altérées chez les femmes ayant eu un DG comparativement aux femmes non-diabétiques (**Tableau 2. 1**).[137] Un total de 21 études sur le sujet ont été identifiées dans cette revue et ont permis de constater des différences dans la composition du colostrum, du lait transitoire et du lait mature des femmes avec DG comparativement aux femmes sans diabète.[137] Certains résultats contradictoires ont été observés, comme pour les contenus en énergie et en protéines du lait qui seraient augmentés, diminués ou sans différence chez les femmes avec DG comparativement aux femmes sans DG selon différentes études.[127, 138, 139] D'autres composantes ont été analysées seulement dans le colostrum de ces femmes, comme le lactose qui se retrouverait en quantité plus faible dans le colostrum des femmes avec DG et les triglycérides (TG) qui auraient des niveaux similaires dans les deux groupes.[139] Différentes hormones ont aussi été étudiées dans le lait de ces femmes, comme l'insuline qui serait augmentée et la ghréline diminuée dans le lait de femmes avec DG selon certaines études[140-143], et des niveaux similaires entre les deux groupes dans d'autres études selon les différents types de lait analysés.[141-144]

Tableau 2. 1 Résultats des différentes études portant sur le diabète gestationnel et la composition du lait humain

Composantes	Effets	Types de lait
Contenu en énergie	Augmenté	Colostrum, lait transitoire et lait mature[127]
	Diminué	Lait mature[138]
Contenu en protéines	Pas de différence	Colostrum[127, 138, 139], lait transitoire et lait mature[138]
	Diminué	Lait transitoire et lait mature[127]
Contenu en glucose	Pas de différence	Colostrum[139]
Contenu en lactose	Diminué	Colostrum[139]
Contenu en lipides totaux	Pas de différence	Colostrum[127, 138], lait transitoire[127, 138] et lait mature[127]
	Diminué	Colostrum[139] et lait mature[138]
Cholestérol	Pas de différence	Colostrum[139]
Triglycérides	Pas de différence	Colostrum[139]

Adapté de Peila et collaborateurs.[137] Traduction libre. Les effets documentés sont ceux retrouvés dans le lait de femmes avec diabète gestationnel (DG) en comparaison au lait maternel de femmes sans DG.

Les auteurs de cette revue ont conclu que le nombre d'études sur le sujet était limité et que les comparaisons entre celles-ci étaient difficiles considérant les méthodes d'analyses variables d'une étude à l'autre, ainsi que les différents types de lait maternel analysés (colostrum, lait transitoire ou lait mature).[137] Plus d'études sont donc nécessaires pour déterminer les composantes du lait maternel affectées par la présence du DG ainsi que l'impact potentiel sur la santé de l'enfant allaité.

2.3 L'introduction des aliments complémentaires

2.3.1 Le moment d'introduction des aliments

Après l'allaitement maternel, l'introduction des aliments complémentaires chez le nourrisson représente une période de changements alimentaires importante qui se produit dans les premiers mois de vie. Le moment recommandé pour introduire les aliments varie généralement entre quatre et six mois selon les différents pays.[80, 145, 146] L'OMS et Santé Canada recommandent l'introduction des aliments complémentaires à partir de six mois.[80, 146] Cependant, selon une étude réalisée en Ontario, quatre femmes sur cinq ne suivraient pas cette recommandation et introduiraient les aliments complémentaires avant l'âge de six mois chez leur enfant.[147]

Il a été suggéré par certains auteurs qu'une introduction précoce des aliments, soit avant l'âge de quatre mois, pourrait contribuer à une augmentation du risque d'obésité chez l'enfant.[6] Cela pourrait s'expliquer par le fait que les apports en protéines sont généralement plus importants lorsque les aliments complémentaires sont introduits, principalement chez les enfants allaités, et qu'un apport élevé en protéines en bas âge serait associé à un IMC plus élevé pendant l'enfance.[109, 148] Il a aussi été suggéré que l'introduction des aliments complémentaires dans le régime alimentaire de l'enfant pourrait entrainer une augmentation de son apport calorique, principalement chez les enfants nourris avec des préparations commerciales pour nourrissons qui auraient plus de difficulté à réguler leurs apports alimentaires selon leurs signaux de faim et de satiété comparativement aux enfant allaités.[149] Cependant, l'association entre le moment d'introduction des aliments et le risque de surplus de poids ou d'obésité demeure controversée. [150, 151] Il est certain qu'en plus du moment d'introduction des aliments, d'autres éléments doivent être pris en considération dans cette association, tel que le type d'aliments offerts à l'enfant.

2.3.2 Le type d'aliments introduits

Mis à part l'introduction des aliments riches en fer qui est à privilégier dès l'âge de six mois, Santé Canada ne recommande plus d'ordre d'introduction des groupes alimentaires chez le nourrisson.[146] Cependant, les jus de fruits, y compris ceux faits de fruits à 100%, ne devraient pas être introduits avant l'âge de 12 mois chez l'enfant.[146] Cet aliment au goût très sucré contient en effet peu de nutriments intéressants pour le bébé en développement, et sa consommation en bas âge pourrait remplacer des aliments plus sains et essentiels à son développement, comme le lait maternel.[152] Ainsi, le type d'aliments introduits à l'enfant pendant cette période critique de son développement pourrait jouer un rôle important sur la programmation de sa santé à plus long terme.

Il a d'ailleurs été suggéré que la période d'introduction des aliments serait une période importante du développement des préférences alimentaires à plus long terme, ce qui pourrait jouer un rôle indirect dans l'état de santé de l'enfant.[7] En effet, dès la naissance, l'être humain a une préférence innée pour les aliments sucrés et présente une aversion pour les aliments au goût amer.[153, 154] D'un point de vue évolutif, il a été suggéré que cette aversion serait un mécanisme de protection contre les aliments potentiellement toxiques. La préférence pour les aliments sucrés, quant à elle, guiderait l'enfant vers des aliments caloriques favorisant sa survie.[153] Ainsi, sous cet angle, il est possible de penser que l'être humain ne soit pas biologiquement conçu pour consommer une saine alimentation telle que décrite aujourd'hui, soit une alimentation riche en légumes et faible en aliments transformés et sucrés. Cependant, d'autres facteurs sont impliqués dans le développement des préférences alimentaires d'un individu, dont l'exposition à différentes saveurs en bas âge.[153]

Mennella et collaborateurs ont conduit de nombreuses études portant sur le développement des préférences alimentaires en bas âge.[115-117, 155] Les résultats de leurs travaux ont permis de démontrer que la saveur des aliments consommés par la mère serait transmise à son enfant par le liquide amniotique lors de la période fœtale ainsi que par le lait maternel au début de sa vie.[117] Par exemple, dans un essai randomisé contrôlé réalisé par ces auteurs, des femmes enceintes planifiant allaiter leur bébé ont été soumis à trois différents groupes.[156] L'un d'eux consommait du jus de carottes pendant le dernier trimestre de la grossesse, le deuxième groupe en consommait pendant les deux premiers mois d'allaitement, et le dernier groupe, constituant le groupe contrôle, ne consommait pas de jus de carottes. Lors du moment d'introduction des aliments chez leur bébé, les enfants ayant été exposés au jus de carottes pendant la grossesse ou l'allaitement maternel acceptaient plus facilement les céréales à saveur de carottes que les enfants du groupe contrôle.[156] Cette étude supporte donc l'hypothèse selon laquelle le développement des préférences alimentaires débuterait très tôt dans la vie de l'enfant via des mécanismes de programmation.[157] Une étude conduite chez la souris a d'ailleurs démontré que l'exposition à certaines flaveurs *in utero* et/ou pendant l'allaitement maternel pouvait moduler le développement du système olfactif du bébé, ce qui entrainerait une meilleure détection et une préférence pour ces mêmes flaveurs plus tard dans la vie.[158] Considérant que les habitudes alimentaires établies en bas âge sont généralement maintenues pendant l'enfance et l'adolescence, il devient intéressant de cibler cette période de plasticité du développement des préférences alimentaires pour de futures interventions visant l'amélioration des habitudes de vie et la prévention de l'obésité.[8, 159]

2.3.3 Introduction des jus de fruits

Tel que mentionné précédemment, Santé Canada recommande d'attendre l'âge de 12 mois avant d'introduire les jus de fruits dans l'alimentation de l'enfant.[146] Bien que depuis 2019, le Guide alimentaire canadien ne reconnaisse plus les jus de fruits comme un constituant du groupe des fruits et légumes, le guide alimentaire de 2007 considérait une portion de 125 mL de jus de fruits comme étant une portion de fruits.[160] Cela pourrait expliquer le fait que les jus de fruits soient consommés en grande quantité chez les jeunes enfants, les parents considérant que cet aliment fasse partie d'une alimentation équilibrée.[161] En effet, parmi les différents groupes d'âges, les enfants âgés de 1-3 ans seraient les plus grands consommateurs de jus de fruits au Canada.[162, 163] Selon les données de l'ESCC de 2004, 62% des garçons et 58% des filles âgés de 1 à 3 ans avaient consommé du jus la veille (selon les données du rappel alimentaire de 24h), comparativement à 39% et 40% chez les garçons et filles du groupe 14 à 18 ans, respectivement.[162] Chez les moins de 18 ans, les adolescents de 14 à 18 ans étaient pour leur part les plus faibles consommateurs de jus de fruits, suivis par les enfants âgés de 4 à 13 qui étaient des consommateurs moyen de ce breuvage.[162] Cependant, selon les données de l'ESCC de 2015, la consommation moyenne de jus de fruits aurait légèrement diminuée parmi tous les groupes d'âges, les enfants de 2 à 17 ans consommant en moyenne une portion de jus de fruits par jour.[164] Somme toute, autant en 2004 qu'en 2015, les enfants sont de plus grands consommateurs de jus de fruits que les adultes.[164]

Population générale

Bien que plusieurs études ne démontrent pas d'effet néfaste du jus de fruits 100% pur sur la santé, la consommation de jus de fruits à un très jeune âge pourrait tout de même avoir des impacts négatifs à long terme sur la santé de l'enfant.[163] Par exemple, dans une étude de cohorte réalisée aux États-Unis (projet Viva), la consommation de jus de fruits à l'âge d'un an a été associée à une plus grande obésité abdominale pendant l'enfance et au début de l'adolescence.[165] De plus, la consommation de jus à l'âge d'un an a été associée à une plus grande consommation de jus et de boissons sucrées pendant l'enfance dans cette même cohorte d'enfants, ainsi qu'à un score Z de l'IMC plus élevé pendant l'enfance.[166] Cependant, la consommation de jus de fruits à un an n'était pas associée au score Z du poids pour l'âge de l'enfant à cet âge, suggérant que l'association entre la consommation de jus en bas âge et un poids plus élevé pendant l'enfance ne serait pas dû à un statut pondéral plus élevé en bas âge qui serait maintenu chez l'individu à travers le temps.[166] En effet, les auteurs ont plutôt suggéré que l'introduction du jus en bas âge entrainerait le développement d'une habitude à la consommation de boissons au goût sucré chez les enfants qui en consomment dès le plus jeune âge, potentiellement dû à un développement des préférences alimentaires dans cette période critique du développement.[153] Dans le même ordre d'idées, des analyses exploratoires réalisées dans le *Project* VIVA ont démontré qu'une introduction précoce des jus de fruits, soit avant quatre mois, était associée à un score Z de l'IMC et un tour de taille plus élevés pendant l'enfance comparativement à ceux ayant reçu du jus pour la première fois plus tard, soit entre 4-6 mois.[167] Les auteurs mentionnent qu'il serait intéressant d'investiguer le rôle d'une introduction précoce du jus sur la consommation de cette boisson plus tard pendant l'enfance.[167] Ainsi, ces précédents résultats et ceux de d'autres études suggèrent que la consommation de jus de fruits en bas âge serait un facteur de risque modifiable du développement de l'obésité et des maladies chroniques à plus long terme, potentiellement via le développement des préférences alimentaires. [168] [169]

Diabète gestationnel

À notre connaissance, aucune étude portant sur l'introduction de jus en bas âge et le développement des préférences alimentaires n'a été réalisée chez les enfants ayant été exposés au DG *in utero*. Cependant, des analyses portant sur la consommation de jus de fruits en bas âge et le risque d'obésité à l'âge de 2-5 ans chez cette population d'enfants ont été réalisées dans la *Study of Women, Infant Feeding and Type 2 Diabetes after GDM* (SWIFT study).[170] Dans cette étude prospective incluant 835 dyades mère-enfant avec une histoire de DG, la consommation de jus de fruits avant l'âge de 12 mois était associée à un risque plus grand d'obésité à l'âge de 2-5 ans et ce, indépendamment de la durée de l'allaitement maternel en bas âge (OR : 2,18, IC 95% : 1,17 – 4,06, p=0,01).[170] De plus, comparativement aux enfants allaités ≥6 mois (pour l'allaitement partiel ou exclusif) et n'ayant pas consommé de jus ou de boissons sucrées pendant les 12 premiers mois de vie, ceux allaités ≥6 mois mais ayant reçu du jus ou des boissons sucrées pendant la première année de vie avaient un risque d'obésité augmenté de trois fois à l'âge de 2-5 ans (OR : 3,32, IC (95% : 1,29 – 8,25) . Parmi les enfants allaités exclusivement pendant ≥6 mois, ceux ayant reçu du jus de fruits en bas âge avait un risque d'obésité à l'âge de 2-5 ans 4,2 fois plus grand (IC 95% :1,6 – 11,2) que ceux ayant été allaités exclusivement pendant six mois mais n'ayant pas reçu de jus avant 12 mois.[170] La consommation de jus et boissons sucrées en bas âge était associée à un risque encore plus grand d'obésité lorsque l'enfant n'avait pas été allaité adéquatement, c'est-à-dire pendant moins de six mois.[170] Les auteurs suggèrent aussi que ces résultats pourraient être expliqués en partie par le développement d'une préférence pour le goût sucré qui pourrait se traduire par une plus grande consommation de boissons sucrées pendant l'enfance, menant à un risque accru d'obésité.[170]

Des résultats utilisant les données du sondage WIC (*Special Supplemental Nutrition Program for Women, Infants and Children*) incluant 3707 participantes, dont 470 avec DG, ont aussi démontré que l'effet de l'allaitement maternel sur le gain de poids de l'enfant pourrait être influencé par la consommation de boissons sucrées en bas âge.[171] En effet, chez les enfants ayant été exposés au DG, l'allaitement exclusif protègerait du risque d'obésité seulement chez les enfants ayant une faible consommation de boissons sucrées alors que chez les enfants non-exposés au DG, l'allaitement maternel aurait un effet protecteur quant au risque d'obésité peu importe la quantité de boissons sucrées consommées en bas âge.[171] Bien que cette étude n'incluait pas les jus de fruits mais seulement les boissons sucrées, elle supporte l'hypothèse selon laquelle l'alimentation en bas âge serait un facteur important à considérer dans la prévention de l'obésité chez les enfants ayant été exposés au DG *in utero*.

Ainsi, agir tôt dans la vie des enfants afin de développer leurs préférences alimentaires et les guider vers une alimentation saine et équilibrée pourrait donc être une stratégie intéressante à considérer chez les enfants exposés au DG.[8] La consommation de jus étant généralisée chez les jeunes enfants, avec près de 60% des jeunes âgés de 1 à 3 ans qui en consomment selon les données canadiennes présentées plus haut, cibler cet aliment au goût sucré pourrait aider à prévenir une préférence pour les boissons sucrées plus tard dans la vie. En effet, bien que les jus de fruits ne soient pas considérés comme étant néfastes pour la santé, comparativement aux boissons sucrées artificiellement, il n'en demeure pas moins qu'ils doivent être consommés avec modération pour faire partie d'une alimentation équilibrée. [163]

2.4 L'alimentation pendant l'enfance

L'alimentation représente un facteur de risque modifiable de différentes problématiques de santé, dont l'obésité et le DT2.[172, 173] D'ailleurs, l'OMS a identifié la promotion d'une saine alimentation chez l'enfant comme une stratégie à mettre de l'avant dans la lutte à l'obésité infantile.[174] La définition d'une saine alimentation peut varier d'un pays à l'autre, mais elle est généralement définie comme une alimentation composée de peu d'aliments transformés riches en sucres et en gras, de beaucoup de fruits et légumes, de protéines végétales et de grains entiers.[172, 173]

2.4.1 Saine alimentation et santé de l'enfant

Population générale

Tel que mentionné plus haut, l'association entre une alimentation de bonne qualité et la santé de l'enfant a été reconnue par différents experts, ce qui a mené l'OMS à inclure la promotion de la saine alimentation dans son plan de lutte à l'obésité infantile.[174] D'ailleurs, dans une revue de Funtikova et collaborateurs, les différentes composantes d'une saine alimentation y sont détaillées et mis en relation avec la santé cardiométabolique des enfants et des adolescents, et la grande majorité des études y démontrent un effet protecteur des composantes d'une saine alimentation sur les risques cardiométaboliques de l'enfant et de l'adolescent.[175] Notamment, il existerait une forte association entre la consommation de fruits et légumes et un risque plus faible d'obésité abdominale chez les enfants d'âge scolaire.[175,

[176] De plus, dans une étude réalisée chez 1764 enfants âgés de 6 à 19 ans, le risque de surplus de poids était réduit chez les plus grands consommateurs de légumes comparativement aux plus faibles consommateurs de ce groupe d'aliments (OR : 0,67, IC 95% : 0,48 – 0,94).[177] Cependant, dans cette étude, les apports en fruits n'étaient pas associés au risque de surplus de poids chez l'enfant.[177] Dans le même ordre d'idées, une étude longitudinale effectuée chez des enfants de 7 à 15 ans a permis de constater que l'adhésion à un patron alimentaire de type élevé en énergie et en lipides et faible en fibres alimentaires était associée à des niveaux d'adiposité plus élevés pendant l'enfance et l'adolescence.[178] De plus, selon une revue systématique publiée en 2020, trois études ont démontré une association entre la consommation d'aliments ultra transformés en bas âge (3-4 ans) et des valeurs plus élevées de cholestérol total, de cholestérol LDL, de triglycérides et de tour de taille plus tard pendant l'enfance (6-8 ans).[179] L'apport énergétique a aussi été positivement associé à la résistance à l'insuline à l'âge moyen de 9 ans.[180]

Ainsi, mis ensemble, les résultats de ces études suggèrent qu'une saine alimentation aurait un effet bénéfique sur la santé de l'enfant dans la population générale. Cependant, il est bien connu que les causes de l'obésité sont multifactorielles et qu'il est généralement impossible de déterminer une seule cause de son développement.[181] Par exemple, tel que souligné au chapitre 1, le développement intra-utérin des enfants exposés au DG les prédispose au risque de développer de l'obésité plus tard dans la vie et ce, même avant leur naissance. Il devient alors intéressant de se demander si les facteurs de risque modifiables qui surviennent pendant la période postnatale, comme la qualité de l'alimentation, pourraient aider à diminuer le risque accru d'obésité et de DT2 chez les enfants ayant été exposés au DG *in utero*.

Diabète gestationnel

Tout d'abord, des analyses réalisées au sein de notre équipe de recherche par Bélanger et collaborateurs ont permis de démontrer que les enfants ayant été exposés au DG consommeraient moins de fruits et légumes que les enfants non-exposés au DG (4,7 ± 2,5 vs 5,4 ± 2,6 portions par jour, p=0,08, respectivement) ainsi que moins de fruits (2,6 ± 1,9 vs 3,2 ± 1,7, p=0,02, respectivement).[182] De plus, dans une étude norvégienne incluant des enfants de 5-8 ans ayant été exposés au DT1 et DG, les enfants exposés au diabète *in utero* atteignaient moins fréquemment la recommandation de consommation de fruits et légumes en vigueur dans ce pays (23% chez les enfants exposés au DG comparativement à 71% pour les enfants du groupe contrôle, p=0,09).[183]

Dans l'étude de Bélanger et collaborateurs, parmi les enfants exposés au DG, ceux qui adoptaient des saines habitudes de vie (définies comme l'adoption de trois comportements sains parmi la consommation de fruits et légumes, la pratique d'activité, la limite du temps d'écran, la limite du temps sédentaire et une durée de sommeil adéquate) avaient tendance à avoir un plus faible pourcentage de gras total et de gras androïde que les enfants exposés au DG avec de moins bonnes habitudes de vie (rencontrant deux comportements sains ou moins).[182] De plus, parmi tous les enfants ayant de moins bonnes habitudes de vie, ceux exposés au DG avaient un plus grand pourcentage de gras total et de gras androïde que les enfants non-exposés au DG *in utero*.[182] Ces résultats suggèrent donc qu'adopter des saines habitudes de vie, y compris une alimentation riche en fruits et légumes, pourrait aider à atténuer les altérations anthropométriques retrouvées chez les enfants exposés au DG. Des conclusions similaires ont été tirées par les auteurs de l'étude *Exploring Perinatal Outcomes among Children*, une étude prospective réalisée aux États-Unis et incluant des enfants exposés ou non-exposés au DG rencontrés pendant l'enfance et l'adolescence.[184] En effet, parmi les enfants ayant un score de la qualité alimentaire <60 (selon le *Healthy Eating Index* (HEI)), ceux ayant été exposés au DG *in utero* avaient des valeurs plus élevées d'IMC, du ratio tour de taille sur tour de hanche, de tissu adipeux viscéral et sous-cutané et de plis cutanés comparativement aux enfants non-exposés au DG *in utero*. Cependant, parmi les enfants ayant un score HEI ≥60, il n'y avait aucune différence significative quant aux mesures anthropométriques des enfants exposés ou non-exposés au DG.[184] Dans le même ordre d'idées, Zhu et collaborateurs ont démontré que le risque de surplus de poids ou d'obésité chez les enfants exposés au DG était plus élevé chez ceux consommant davantage de boissons sucrées (RR : 1,59, IC 95% 1,05 – 2,40), un indicateur d'une alimentation de moins bonne qualité, comparativement à ceux qui en consommaient moins pendant l'enfance (RR : 1,10, IC 95% : 0,81- 1,48).[58]

Ainsi, bien que limitées, les études sur le sujet semblent indiquer qu'une saine alimentation pourrait être associée à un meilleur profil anthropométrique chez l'enfant né d'une grossesse compliquée par un DG. Cependant, plus d'études sur le sujet sont nécessaires pour confirmer cette association et devraient inclure le rôle de l'alimentation dans la prévention d'autres complications de santé, tel que le DT2. Des stratégies permettant d'améliorer la qualité de l'alimentation devraient aussi être explorées, considérant que les enfants ayant été exposés au DG *in utero* semblent avoir une alimentation de qualité moindre comparativement aux enfants nés de grossesses en santé. Pour ce faire, il serait intéressant d'étudier les déterminants de la saine alimentation chez les enfants de cette population spécifique.

2.5 Les déterminants de la saine alimentation chez l'enfant

L'écart entre les recommandations alimentaires établies par les instances de santé et l'alimentation réelle des individus s'explique par le fait que différents facteurs influencent les choix alimentaires d'un individu. En effet, les lignes directrices du Guide alimentaire canadien définissent une alimentation qui permettrait d'atteindre un état de santé physique optimal chez un individu, mais l'état de santé ne représente pas nécessairement un facteur qui influence positivement les choix alimentaires de tous. En effet, selon le modèle écologique du développement humain de Bronfenbrenner, les comportements humains dépendraient de différents facteurs personnels et environnementaux, ainsi que de leurs interactions.[185] Ce modèle conceptuel a été utilisé par plusieurs auteurs pour identifier les déterminants des choix alimentaires des individus, y compris ceux des enfants.[186, 187] Dans le modèle proposé par de Cosmi et collaborateurs (**Figure 2. 1**), on constate que différents facteurs inhérents à l'enfant et externes à celui-ci sont susceptibles d'influencer ses habitudes alimentaires.[186]

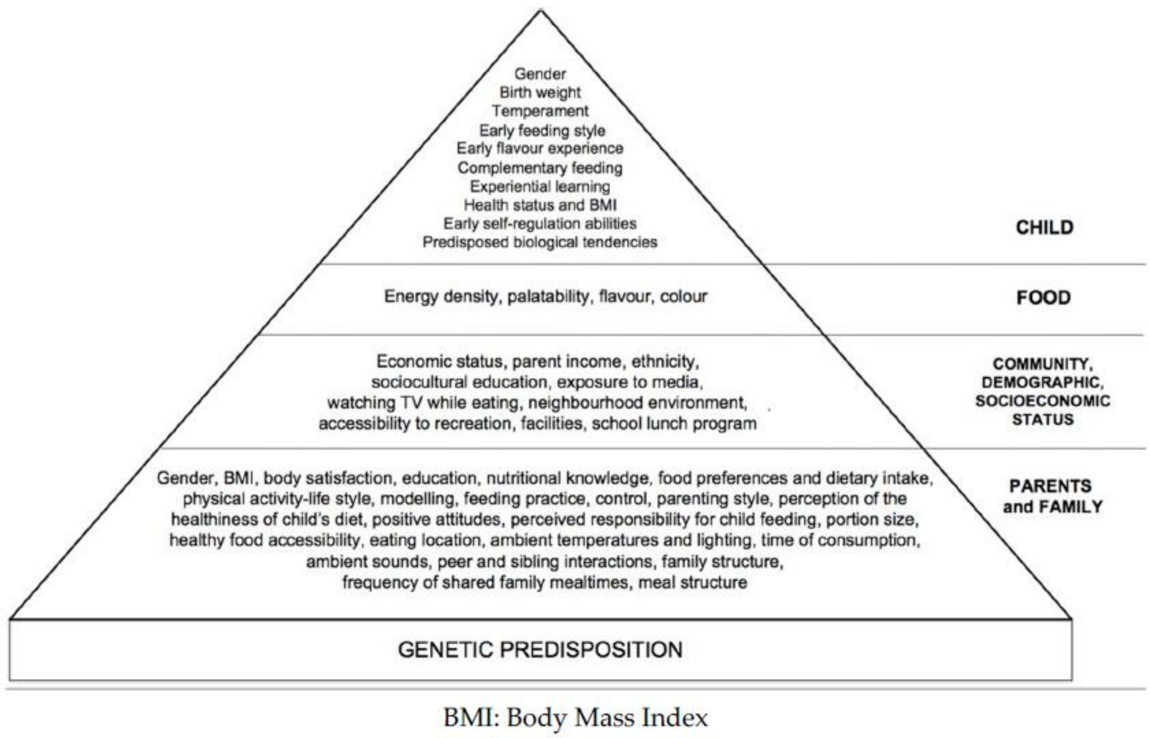

Figure 2. 1 Facteurs influençant les habitudes alimentaires des enfants [186]

2.5.1 Facteurs individuels

Population générale

Parmi les facteurs inhérents à l'enfant, l'alimentation en bas âge pourrait influencer ses habitudes alimentaires. En effet, tel que décrit dans la section 2.3 de ce chapitre, les préférences alimentaires de l'enfant sont établies tôt dans la vie et sont modulées par les expériences alimentaires qui se produisent dans cette période précoce du développement, comme l'allaitement maternel ou l'introduction des aliments complémentaires, ce qui peut influencer ses préférences alimentaires à plus long terme.[153] D'ailleurs, les préférences alimentaires seraient un des facteurs les plus importants des choix alimentaires réalisés par l'enfant, d'où l'importance d'agir dès le plus jeune âge afin de prévenir l'aversion des aliments sains ou une préférence pour les aliments sucrés et salés chez ceux-ci.[188]

D'autres facteurs individuels mais non modifiables, comme l'âge et le genre de l'enfant, pourraient aussi influencer ses habitudes alimentaires.[187, 189] En effet, selon une étude réalisée chez des jeunes d'âge scolaire primaire et secondaire, les filles aimeraient davantage les fruits et légumes que les garçons, alors que ces derniers préféreraient les aliments gras et sucrés ainsi que les viandes et substituts.[189] Les auteurs de cette étude ont suggéré que ces différences pourraient être liées aux construits sociaux voulant que les filles accordent d'avantage d'importance à une saine alimentation que les garçons.[189] De plus, pendant l'enfance et l'adolescence, l'âge serait négativement associé à la qualité de son alimentation selon certaines études. [190, 191] Cela pourrait s'expliquer par le fait que plus l'enfant vieillit et devient mature, moins il sera contraint à suivre les choix alimentaires de ses parents et plus il serait apte à décider lui-même ce qu'il aimerait manger, principalement à l'extérieur de la maison. Tel que mentionné plus haut, ses choix seront grandement influencés par ses préférences alimentaires[188], ce qui pourrait entrainer une plus grande consommation d'aliments sucrés et salés. [189, 192]

Diabète gestationnel

À notre connaissance, aucune étude réalisée spécifiquement chez les enfants ayant été exposés au DG *in utero* n'a été conduite afin d'identifier les déterminants individuels de la saine alimentation chez ceux-ci. Considérant que ces enfants semblent être exposés dès le plus jeune âge à des expériences alimentaires différentes, par exemple par une plus courte durée d'allaitement, ou considérant leur risque accru d'obésité, il est pertinent de se demander si les déterminants de la saine alimentation identifiés dans la population générale sont aussi associés à la qualité de l'alimentation de cette population d'enfants. Les résultats du chapitre 9 de cette thèse avaient ainsi pour objectif de répondre à cette question.

2.5.2 Facteurs environnementaux

Population générale

L'environnement dans lequel l'enfant grandit influence aussi grandement ses comportements alimentaires.[187] Les aliments disponibles à la maison, les repas pris en famille ou devant une écran, la composition de la famille ou encore les apports alimentaires des parents sont des facteurs importants de l'environnement alimentaire de l'enfant à considérer.[187] Par exemple, plusieurs études ont démontré que le nombre de repas pris en famille serait associé à la qualité de l'alimentation de l'enfant.[193, 194] De plus, selon une méta-analyse, l'âge de l'enfant, le pays d'origine, le nombre de membres de la famille présents aux repas ainsi que le type de repas pris en famille (déjeuner, diner ou souper) n'influenceraient pas l'association entre la fréquence des repas pris en famille et la qualité de l'alimentation de l'enfant.[194] Différentes hypothèses ont été émises pour expliquer cette association, notamment le fait que les repas mangés en famille sont souvent cuisinés et donc, de meilleure qualité que les repas pris à l'extérieur de la maison.[194] Les interactions entre les membres de la famille lors du repas, par exemple pour discuter des aliments et de la saine alimentation, seraient aussi d'importants contributeurs au développement d'une saine alimentation chez l'enfant.[187] Cela pourrait expliquer pourquoi les repas pris en famille devant la télévision n'auraient pas le même impact sur la qualité globale de l'alimentation de l'enfant.[195] En effet, les repas pris devant un écran auraient plutôt comme effet d'entrainer une suralimentation, l'enfant étant moins à l'écoute de ses signaux de satiété lors du repas, et pourraient influencer ses choix alimentaires vers des aliments moins sains sous l'influence des annonces publicitaires qui en font souvent la promotion.[196]

Les parents jouent aussi un rôle important dans l'établissement des habitudes alimentaires de leurs enfants. Plusieurs études ont établi une association entre les apports en fruits et légumes de la mère et ceux de son enfant. [197-200] Cela pourrait s'expliquer par le fait que la mère est souvent la principale personne responsable des aliments disponibles à la maison, expliquant pourquoi ses apports alimentaires ressemblent à ceux de son enfant. [201] Cependant, certains auteurs suggèrent aussi que la mère jouerait un rôle de modèle dans le développement des habitudes alimentaires de son enfant, influençant donc positivement son apport en fruits et légumes si elle-même en consomme et prend plaisir à en consommer.[202] Malheureusement, le rôle du père comme modèle dans le développement des habitudes alimentaires des enfants a très peu été étudié dans la littérature actuelle, mais il est possible de penser que ce dernier pourrait aussi influencer la qualité de l'alimentation de son enfant.[187] D'autres facteurs externes à l'enfant peuvent entrer dans l'équation du développement des préférences alimentaires, comme le revenu familial ou encore le niveau d'éducation des parents. En effet, un statut socioéconomique élevé chez les parents serait associé à une meilleure qualité alimentaire des enfants, possiblement dû à un meilleur salaire permettant d'acheter des aliments de meilleure qualité ou encore à de meilleures connaissances en nutrition. [203-209]

Finalement, des pratiques parentales positives et non-restrictives seraient aussi associées à une meilleure qualité alimentaire chez l'enfant.[210]

Diabète gestationnel

Tout comme pour les facteurs individuels, il n'existe pas, à notre connaissance, d'étude ayant évalué l'association entre les déterminants environnementaux de la saine alimentation et la qualité de l'alimentation des enfants ayant été exposés au DG. Cependant, ces enfants gravitent dans un environnement alimentaire souvent différent de celui des enfants non-exposés au DG *in utero*. Notamment, plusieurs études ont démontré que les femmes ayant eu un DG auraient une alimentation de moins bonne qualité que les femmes sans DG, ce qui laisse supposer une moindre grande disponibilité d'aliments sains dans l'environnement de leurs enfants.[211-213] Ainsi, il serait pertinent d'étudier l'association entre les déterminants environnementaux des apports alimentaires des enfants identifiés dans la littérature et la qualité de l'alimentation des enfants de cette population spécifique afin d'établir des stratégies de promotion des saines habitudes de vie efficaces et adaptées à eux.

Chapitre 3 Objectifs et hypothèses

À ce jour, peu d'études ont permis d'identifier des stratégies de prévention efficaces des complications associées à une exposition intra-utérine au DG, comme le DT2 ou l'obésité. En effet, bien que plusieurs études aient démontré une association entre l'allaitement maternel et une diminution du risque de surplus de poids ou d'obésité pendant l'enfance, certaines études présentent des résultats contradictoires et le rôle de la composition du lait maternel des femmes avec DG est peu étudié pour expliquer ces résultats. De plus, très peu d'études ont évalué le rôle de l'alimentation pendant la petite enfance et l'enfance sur la santé des enfants ayant été exposés au DG. Comme les femmes ayant eu un DG et leurs enfants ont généralement de moins bonnes habitudes alimentaires que la population générale, il devient pertinent d'étudier les facteurs pouvant influencer la qualité de l'alimentation de cette population d'enfants, dans le but ultime d'établir des stratégies de prévention de l'obésité et du DT2 qui soient efficaces et adaptées à ceux-ci.

Ainsi, **l'objectif général** de cette thèse de doctorat était d'étudier le rôle de l'alimentation dans la prévention des complications associées à une exposition intra-utérine au DG. Plus spécifiquement, l'allaitement maternel et la composition du lait maternel ont été étudiés, de même que l'introduction des jus de fruits en bas âge, la qualité de l'alimentation pendant l'enfance ainsi que les déterminants de la saine alimentation chez l'enfant.

Au **chapitre 4**, l'objectif était de présenter de façon systématique les études portant sur l'association entre l'allaitement maternel et le risque d'obésité chez les enfants ayant été exposés au DG *in utero*.

L'objectif du **chapitre 5** était d'étudier l'association entre l'allaitement maternel et la courbe de croissance de 0 à 5 ans selon le statut d'exposition au DG *in utero*. L'hypothèse émise était que l'allaitement maternel serait associé à une courbe de croissance plus lente chez les enfants non-exposés comparativement à ceux exposés au DG *in utero*.

L'objectif du **chapitre 6** quant à lui était de comparer la composition du lait maternel en macronutriments chez des femmes avec et sans DG et d'évaluer l'association entre la composition du lait et la croissance de l'enfant de la naissance à deux mois. Nous avons émis l'hypothèse que la composition du lait maternel serait différente entre les deux groupes, principalement avec des niveaux plus élevés de triglycérides et lactose chez les femmes avec DG, et que la composition du lait influencerait la croissance des enfants, indépendamment du statut de DG de la mère. Plus spécifiquement, nous émettons l'hypothèse que les niveaux de protéines seront associés positivement au gain de poids des enfants alors que les niveaux de triglycérides seront associés négativement aux mesures pondérales des deux groupes.

Au **chapitre 7**, l'objectif était d'évaluer l'association entre une introduction précoce des jus de fruits chez le bébé et la consommation d'aliments et boissons au goût sucré pendant l'enfance chez des enfants exposés ou non-exposés au DG. L'hypothèse émise était qu'une introduction précoce des jus est associée à une plus grande consommation d'aliments et boissons au goût sucré pendant l'enfance dans les deux groupes.

L'objectif du **chapitre 8** était d'étudier l'association entre la qualité de l'alimentation et les profils glycémique et anthropométrique des enfants exposés ou non-exposés au DG *in utero*. L'hypothèse émise était qu'une meilleure qualité de l'alimentation est associée à de meilleurs profils glycémique et anthropométrique chez ces enfants.

Finalement, au **chapitre 9**, l'objectif était d'évaluer l'association entre différents déterminants individuels et environnementaux de la qualité de l'alimentation identifiés dans la littérature et la qualité de l'alimentation des enfants exposés ou non-exposés au DG *in utero*, ainsi que d'étudier l'association entre la qualité de l'alimentation de la mère et celle de son enfant. Nous avons émis l'hypothèse que les déterminants individuels et environnementaux sont associés à la qualité de l'alimentation des enfants des deux groupes et que les apports en fruits et légumes de la mère sont associés à ceux de son enfant.

Afin de répondre à ces objectifs, les résultats de deux projets de recherche distincts ont été utilisés. Le premier projet, le projet GDM2, est une étude transversale qui incluait des femmes avec ou sans antécédent de DG et leurs enfants exposés ou non-exposés *in utero* au DG. Il avait pour but d'évaluer l'impact du DG sur la santé de la femme et de son enfant, et de mieux comprendre le rôle des facteurs postnataux dans la prévention des complications associées au DG. Le projet s'est déroulé entre 2012 et 2017 et les rencontres ont eu lieu à l'Institut sur la nutrition et les aliments fonctionnels (INAF). Brièvement, les femmes et leurs enfants nés entre 2003 et 2013 étaient invités à participer à une seule rencontre, à l'unité d'investigation clinique de l'INAF, afin de compléter différents tests et questionnaires, y compris une analyse de la composition corporelle, une prise de sang à jeun ainsi que la complétion de questionnaires alimentaires. Les méthodes détaillées de cette étude sont décrites dans les articles présentés aux chapitre 5, 7, 8 et 9 de cette thèse.

Pour atteindre l'objectif présenté au chapitre 6, les échantillons de lait maternel du projet pilote d'une intervention visant la modification des habitudes de vie en période postpartum chez des femmes ayant eu un DG (projet DÉPART) ont été utilisés. Ces femmes ont été recrutées pendant la grossesse et étaient invitées à participer à la première rencontre du projet deux mois après l'accouchement. Lors de cette rencontre, différents tests et questionnaires ont été administrés, comme un test de tolérance au glucose, une mesure de la composition corporelle ainsi qu'une collecte de lait maternel. Le poids du bébé de la naissance à deux mois a été documenté dans le carnet de santé de celui-ci. Des femmes sans antécédent de DG ont par la suite été recrutées et soumises à la même rencontre que les femmes du projet DÉPART, deux mois après l'accouchement, permettant ainsi l'ajout d'un groupe contrôle à l'étude. Les méthodes détaillées de ce projet sont décrites dans l'article présenté au chapitre 6 de cette thèse.

Chapitre 4 Rôle de l'allaitement maternel dans la prévention de l'obésité chez les enfants nés de femmes avec diabète gestationnel : une revue systématique de la littérature

Camille Dugas, Mélissa Bélanger et Julie Robitaille.

L'article présenté dans ce chapitre s'intitule: *Role of breastfeeding in obesity prevention in children born from mothers with gestational diabetes mellitus: a systematic review*

Il a été soumis pour publication à la revue *Childhood Obesity* le 30 août 2021.

Résumé

But: Résumer les connaissances actuelles quant à l'association entre l'allaitement maternel et les mesures reliées à l'obésité chez les enfants ayant été exposés au DG *in utero.*

Méthodes: Les bases de données *Medline*, *Embase* et *Web of Science* ont été utilisées pour identifier les études éligibles entre juillet 2020 et mars 2021. La lecture des titres et résumés (n=655) et des textes entiers (n=59) a été réalisée simultanément par deux réviseurs indépendants. L'extraction des données a été réalisée par un réviseur et vérifiée par le second. La qualité des études a été évaluée par les deux réviseurs et la concordance des scores attribués a été vérifiée.

Résultats: Un total de 16 études a été inclus, avec 25% d'entre-elles ayant reçu un score de la qualité considéré comme « fort ». L'allaitement était associé à des mesures liées à l'obésité plus faibles pendant l'enfance et l'adolescence dans certaines études (n=6), bien que certaines études n'aient démontré aucune association entre l'allaitement et l'obésité pendant cette période (n=4). Pendant la petite enfance (<2 ans), les études présentaient des résultats contradictoires, avec trois études démontrant une association négative entre l'allaitement maternel et les mesures liées à l'obésité, et trois autres études ne démontrant aucune association. Cependant, seulement deux études sur 16 ont démontré une association positive entre l'allaitement maternel et le poids ou gain de poids des enfants, une pendant la petite enfance et l'autre pendant l'enfance. Finalement, il y avait seulement deux études portant sur l'association entre la composition du lait et la croissance de l'enfant.

Conclusion: Cette revue souligne que l'allaitement maternel semble être associé à des mesures du profil anthropométrique plus faibles chez les enfants exposés au DG pendant l'enfance et l'adolescence, mais plus d'études de bonne qualité sont nécessaires pour confirmer ces résultats.

Abstract

Aim: To summarize current knowledge regarding the association between breastfeeding and obesity related outcomes in children exposed to GDM *in utero* (GDM+).

Methods: Medline, Embase and Web of Science were searched to identify relevant studies on this topic between July 2020 and March 2021. Screening of titles and abstracts (n=655), and full texts (n=59) were done simultaneously by two independent reviewers. Data extraction was done by one reviewer and verified by the second. Quality assessment was conducted by the two reviewers and concordance was verified.

Results: A total of 16 studies met the inclusion criteria, with 25% of them that received a strong quality rating. Breastfeeding was associated with reduced obesity related outcomes during childhood and adolescence in some studies (n=6), although other studies showed no association between breastfeeding and obesity in this period (n=4). During infancy (<2 years), studies showed mixed results, with three studies showing a negative association between breastfeeding and obesity-related outcomes while three others showed no association. However, only two studies out of 16 showed a positive association between breastfeeding and growth, one during infancy and one during childhood. Finally, there were only few studies assessing the association between breast milk composition and infant growth (n=2).

Conclusion: This review highlighted that breastfeeding seemed to be associated with a better anthropometric profile among GDM+ children, mainly during childhood and adolescence, but that additional studies of strong quality are needed to confirm this finding.

Title page

Role of breastfeeding in obesity prevention in children born from mothers with gestational diabetes mellitus: a systematic review

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Introduction

Gestational diabetes mellitus (GDM), defined as hyperglycemia with first onset or recognition during pregnancy [1], is a known risk factor for childhood obesity [2]. Given the high prevalence of GDM[3] and health consequences of childhood obesity [4, 5], there is an urgent need to find efficient strategies targeting modifiable factors to prevent obesity among these high-risk children.

Breastfeeding has many known benefits for both mother and children, including the prevention of obesity among breastfed infants [6, 7]. Indeed, many studies conducted in the general population showed that breastfeeding is associated with lower risk of obesity, with a dose-dependent effect where each additional month of breastfeeding is associated with a greater risk reduction [8]. On the other hand, the effect of breastfeeding on the prevention of obesity among children born from mother with GDM is quite unclear. Indeed, while many studies showed a protective effect of breastfeeding on obesity development in this population[9-12], others found opposite results[13, 14]. Among them, Plagemann et al. showed that breastmilk (BM) intake from diabetic mothers (either GDM or type 1 diabetes) in the first week of life was associated with higher body mass index (BMI) at two years of age, probably due to an altered composition of diabetic BM [14].

To our knowledge, the only few existing literature reviews regarding the association between breastfeeding and obesity prevention in offspring of diabetic mothers are non-systematic or included different types of diabetes (pre-existing type 1 and 2 and GDM), or evaluated the effect of breastfeeding on growth during infancy only (<2 years), i.e. not later in childhood and adolescence [15-18]. Thus, to address the need to summarize, in a systematic manner, current knowledge on this topic, the objective of this systematic review was to investigate the role of breastfeeding on the prevention of obesity in children exposed to GDM in utero (GDM+ children). The duration and exclusivity of breastfeeding was considered and its impact on obesity prevention from infancy to adolescence was compared between GDM+ and GDM- children, or between GDM+ children with different history of breastfeeding. Studies addressing BM composition of women with prior GDM in relation to children's growth were also included to identify possible mechanisms underlying findings of this review.

Material and Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA) [19] and the study protocol was registered in PROSPERO (CRD42021234008).

Search strategy

A total of three databases were searched, namely *Medline/Pubmed*, *Embase* and *Web of Science*. The search strategy for each database was developed in collaboration with a specialised scientific librarian and was conducted on July 30th, 2020 with bimonthly updates of the literature until March 2021. No publication year limit was defined for this review but only publications in English or French were included. The search strategy was based on four main topics, i.e. gestational diabetes mellitus, breastfeeding, obesity and the period of life (infancy, childhood and adolescence). Exhaustive list of synonyms for these four topics were searched in uncontrolled vocabulary in each database and in controlled vocabulary in Medline and Embase. The search strategy in Medline was as following: '((Breastfeeding OR breast feeding OR breast milk OR breastmilk OR human milk OR infant feeding OR colostrum) OR Breast Feeding/ OR Milk, Human/) AND ((Gestational diabetes mellitus OR diabetes induced pregnancy) OR Diabetes, Gestational/) AND ((Obes* OR overweight OR fat mass OR fatmass OR bodyfat OR body fat OR anthropometric profile OR adiposity OR bodyweight OR body weight OR weight OR BMI OR body mass OR bodymass) OR obesity/ OR obesity, abdominal/ OR Pediatric Obesity/ OR Body Weight/ OR Overweight/) AND ((infant OR infants OR child* OR adolescen* OR toddler OR pediatr* OR peadiatr* OR schoolchild OR preschool* OR pre-school* OR schoolage* OR school-age* OR preteen* OR pre-teen* OR teen* OR youth OR young person OR young people) OR adolescent/ OR child/ OR child, preschool/ OR infant/). Finally, references of included articles and pertinent literature reviews were also screened.

Eligibility criteria (PICOS)

Population

Studies that included children exposed to GDM in utero (no other type of diabetes) were included. If the study included different types of diabetes, only those with separate analyses for different types of diabetes were included. Studies including children aged of less than 18 years were selected.

Intervention or exposure

The exposure consisted of breastfeeding (yes or no) or duration or intensity (exclusivity) of breastfeeding. Exposition to specific components of BM was also studied.

Comparison

Comparison group was GDM- children with the same breastfeeding exposure or GDM+ children not breastfed or breastfed less longer (exclusively or not).

Outcomes

Included studies had to provide information on children's anthropometric measurements in infancy, childhood, or adolescence in relation to the breastfeeding exposure. Obesity or overweight prevalence were considered as eligible main outcomes, as well as BMI z-score, weight-for-age z-score, weight gain, waist circumference or body composition. Thus, main findings were prevalence, relative risk, or mean difference between groups, depending on the outcome of the study.

Study design

This review included cohort and cross-sectional studies. No intervention study on this topic was available.

Study selection

All articles resulting from searches in the three databases were imported in Covidence software (Veritas Health Innovation) and duplicates were automatically removed. The screening of titles and abstracts was conducted in Covidence by two independent reviewers

(CD and MB) and was followed by the screening of full text articles by the same two reviewers. A third reviewer (JR) was available if conflicts occurred in the screening process. The decision to include a study in the systematic review was based on the PICOS (population, intervention or exposure, comparison, outcome, and study design) selection criteria.

Data extraction and quality assessment

Data extraction and quality assessment were done simultaneously by CD. Data extraction for each article was validated by MB. The third reviewer was available to resolve potential conflicts, if needed. Data extraction was conducted using a standardized extraction form. The following information was extracted for each study: authors name and year of publication, aim, study design, study population, GDM diagnosis criteria, breastfeeding measures, obesity related outcomes, children’s age at outcome measurements and main findings. Missing information were obtained by contacting the corresponding authors of manuscripts, when needed. Finally, main findings were further separate according to the age of children (infancy, childhood, and adolescence).

Quality of included studies was assessed using the Effective Public Health Practice Project’s (EPHPP) quality assessment tool for quantitative studies [20, 21]. This tool has been developed to assess quality of studies in the field of public health and therefore, is not restricted to randomized controlled trial quality assessment. The EPHPP quality assessment tool score is based on six different criteria, namely 1) selection bias; 2) study design; 3) confounders; 4) blinding; 5) data collection methods; and 6) withdrawals and dropouts. A global score is finally assessed using these 6 underscores. To be considered as studies with strong quality, studies must have no weak underscore; studies of moderate quality have only one weak rating, and studies of weak quality have two or more weak ratings[21]. Both CD and MB evaluated quality of studies independently and there was 88% concordance in the global scores assigned by the two reviewers. Agreement for the two studies with discordant global scores was obtained afterwards by CD and MB.

Results

Results of the search strategy are presented in Figure 1 following the PRISMA flow chart [19]. Overall, of the 655 studies screened, 16 met the inclusion criteria for the qualitative review [9-13, 22-32]. Details regarding study design, methods and main results of included studies are presented in Table 1. Given the heterogeneity of methods used to define breastfeeding and obesity related outcomes across included studies, as well as various ages at outcomes measurements, no meta-analysis of the pooled results was conducted.

Characteristics of studies

All included studies were observational, with 11 (69%) that were cohort studies [9, 13, 24-32] and five (31%) that had a cross-sectional study design [10-12, 22, 23]. Two studies reported results from the Study of Women, Infant Feeding and Type 2 Diabetes Mellitus after GDM pregnancy and the Growth of their Offspring (the SWIFT Offspring Study) [9, 31]. Two other studies used data from the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) survey in their article [11, 12]. Finally, two studies reported data from the same study population of Canadian children aged between 2-14 years [22, 23]. Almost all studies (14 out of 16) aimed at evaluating the association between breastfeeding in early life and obesity related outcomes in infancy, childhood, or adolescence [9-13, 22, 23, 25-31].Two studies aimed at evaluating the association between BM composition and growth of GDM+ children [24, 32]. All studies were published after 2000 with only two studies published before 2010 [10, 29].

Characteristics of participants

Almost all studies were conducted among GDM+ children only, although two studies included children exposed to pre-existing diabetes in their participants [27, 29]. However, separate analyses for GDM+ children were presented in these two studies and only these results were included in the current review. Criteria for GDM diagnosis varied between studies. Indeed, some studies used guidelines from their respective country, three studies used the Carpenter and Coustan criteria [9, 31, 32] and three others included women with a self-reported GDM history [11, 12, 26]. A total of nine studies presented results during infancy (<2 years of age) [9, 12, 13, 23-26, 28, 32], 11 studies showed results for the childhood period [10-13, 22, 23, 26, 27, 29-31] and only three studies included adolescents (≥12 years) [22, 26, 30].

Breastfeeding measures

Classification of breastfeeding differed across studies where breastfeeding duration was studied as a continuous variable [22, 23, 28], or dichotomized into groups using different cut-offs [10-13, 31]. Others classified children according to a breastfeeding status, i.e. no BF, partial breastfeeding or exclusive breastfeeding [25-27, 29]. In one study, the mean volume of milk ingested per day in the first week of life was estimated by weighting the infant before and after every nursing for this period [29].

The use of a breastfeeding score that combined duration and exclusivity of breastfeeding was seen in four studies [9, 13, 30, 31]. Among them, two studies used a similar score that was defined as the sum of months of exclusive breastfeeding with the multiplication of months of partial or predominant breastfeeding by its respective breastfeeding weight, which result in a milk month value [13, 30]. Breastfeeding weight was calculated according to the intensity of breastfeeding, where exclusive formula feeding has a weight of 0, exclusive breastfeeding has the maximal weight, and partial and predominant breastfeeding weights are between these extreme values. Two studies used the Piper and Parks score [33], where the number of milk feeds per day was divided by the number of all liquids fed in the past seven days, resulting in a fractional score where 0 represents exclusive formula feeding and 1 exclusive breastfeeding [9, 31].

Finally, as mentioned above, two studies [24 32] that evaluated the impact of BM composition on children's growth were included. One of them evaluated levels of irisin and SREBP-1c in colostrum and mature milk of GDM mothers while the other evaluated the adiponectin, leptin, insulin and ghrelin concentrations in colostrum and mature BM milk [24, 32].

Obesity related outcomes

Different anthropometric measurements were used to assess the association between breastfeeding and children's growth. The risk of overweight and obesity was described in five studies [10-12, 27, 31], although definition of overweight and obesity varied between studies. Many studies used BMI, BMI z-score or BMI SDS to describe anthropometry of children [13, 22, 25, 26, 30,] while others used weight, weight-for-age z-score or weight gain during a specific period of time [9, 13, 22-25, 28, 29, 32]. Finally, measures of adiposity, including waist circumference, body fat mass and skinfold thickness, were described in only three studies [9, 22, 30].

Quality assessment of studies

Only four studies (25%) were rated as being of strong quality [26, 30-32], 7 (44%) were of moderate quality (n=7; 44%) [9, 13, 23-25, 27, 28] and the remaining five studies (31%) were rated as weak [10-12, 22, 29]. Among others, main reasons to obtain a weak score were the cross-sectional study design, the presence of selection bias in the recruited population or the lack of statistical adjustment for important confounders.

Results from studies

Overall, majority of studies that assess the association between breastfeeding (duration and/or exclusivity) found a negative association between breastfeeding and anthropometric profile of children, as shown in Table 2. Results presented in Table 2 are separated into categories according to children's age, i.e. infancy or childhood and adolescence, explaining why some studies reporting results from both periods are presented twice in this table. Furthermore, given that studies conducted by Fatima et al. [24] and Yu et al. [32] did not evaluate the practice of breastfeeding but rather studied the effect of specific components of BM on infant growth, their results were not included in Table 2.

Thus, results from 8 different studies [9-12, 25, 27, 30, 31] showed a protective effect of breastfeeding on obesity related outcomes either in infancy or childhood, while five others [13, 22, 23, 26, 28] found no association (Table 2). Furthermore, only two studies [13, 29] showed adverse effects of breastfeeding on weight gain in the first 6 months of life or on body weight at 2 years, respectively. However, further analyses in these two studies showed either no association between breastfeeding with weight trajectory from birth to 36 months [13] or no association between breastfeeding status at 2-4 weeks of life and body weight at 2 years after adjustment for BM intake in the first week of life [29].

During the infancy period, the association between breastfeeding and anthropometric profile of infant was either negative (n=3) [9, 12, 25] or null (n=3) [23, 26, 28] in majority of studies. On the other hand, during childhood and adolescence, six studies out of 11 (55%) showed negative association between breastfeeding practices and obesity related outcome of GDM+ children [10-12, 27, 30, 31] while four studies showed a null association [13, 22, 23, 26].

Finally, only two studies showed associations between BM composition and children's growth [24, 32]. Both studies found that BM composition of women with GDM+ differed than women with GDM-, which could influence infant's growth [24, 32]. Indeed, GDM+ women had lower levels of irisin and adiponectin in their colostrum and mature BM [24, 32]. Irisin level was positively associated with the weight of babies at 6 weeks of life [24] while adiponectin was associated with lower weight-for-age at 3 months of life [32].

Discussion

In this systematic review, most studies suggested that breastfeeding was associated with a better anthropometric profile in GDM+ children, a specific population at high-risk of obesity. This was particularly true during childhood and adolescence, while studies conducted in infancy showed mixed results. However, in both periods, a considerable number of studies showed no association between breastfeeding and obesity related outcomes, highlighting the need for more studies of good quality to confirm the beneficial effects of breastfeeding on obesity prevention in this population. Nevertheless, it should be noted that only two studies showed a positive association between breastfeeding and obesity related outcomes in GDM+ offspring, and that these results seemed to be only transitory. Finally, there was a lack of studies assessing the association between BM composition of mothers with previous GDM and children's growth.

Childhood and adolescence

Majority of studies conducted in childhood and adolescence showed a negative association between breastfeeding and obesity related outcomes [10-12, 27, 30, 31]. Among them, Schaeffer-Graf et al. showed that exclusive breastfeeding for more than three months was associated with a reduced risk of overweight in GDM+ children aged between 2-8 years compared to those breastfed less longer [10]. Furthermore, in two studies conducted by Vandyousefi et al. [12, 31], exclusive breastfeeding for <6 months was associated with a higher risk of obesity during childhood. These studies are in accordance with studies conducted in the general population [8]. On the other hand, other authors cited in this review added a nuance to their results. For example, Kaul et al. showed that the beneficial effect of breastfeeding on overweight or obesity risk reduction was only seen in GDM+ children that were born AGA, but not in LGA infant, while breastfeeding was associated with a risk reduction of obesity in both AGA and LGA children born from non-diabetic mothers [27]. Moreover, Shearrer et al. showed that breastfeeding during more than 12 months only was associated with a reduced risk of obesity in GDM+ children, while any breastfeeding duration was associated with obesity risk reduction in GDM- children [11]. This suggested that even if breastfeeding is associated with a better anthropometric profile in GDM+ children, a longer duration seemed necessary to be associated with a reduced risk of obesity in this population, in comparison to GDM- children. Thus, further investigations should be conducted to better understand these findings.

Infancy

During infancy, three of the seven studies showed a negative association between breastfeeding and obesity related outcome while three others showed no association, and the remaining one showed a positive association between breastfeeding and growth. Gunderson et al. showed that children with higher breastfeeding score, which imply longer duration and exclusivity, had a lower increase in weight-for-length and weight-for-age z scores from birth to 12 months of life compared to those with a lower breastfeeding score [9]. Similarly, Fenger-Grøn et al. found that breastfeeding was associated with a lower BMI SDS from birth to 5 months [25]. These results are similar to studies conducted in the general population [34]. On the other hand, Hui et al. found no significant interaction between GDM status, breastfeeding status in the first three months of life and BMI z-score from three to nine months of age [26]. Kramer et al. also showed no association between breastfeeding duration and weight gain from birth to three months of life [28]. Finally, Aris et al. found a positive association between breastfeeding for 4 months or more and higher growth trajectory in the first 6 months of life [13]. Thus, with the heterogeneity of results presented in this review, it is difficult to determine whether breastfeeding is associated with a reduced growth in early life among GDM+ children.

Breast milk composition

This review highlighted that very few studies assessed the association between BM composition in the context of previous GDM and infant growth. The only two studies in this review pointed towards differences in BM composition in the context of GDM that could affect infant's growth. Fatima et al. showed that mature BM of GDM women had lower levels of irisin compared to women without GDM and that irisin levels were positively associated with weight at 6 weeks of life in the entire cohort (GDM+ and GDM- combined) [24]. These results suggest an adaptation of BM composition in the context of recent GDM that may help the infant to prevent its later risk of obesity. On the other hand, Yu et al. found lower levels of adiponectin in BM of GDM women, and that adiponectin in BM was associated with lower weight-for-age at three months in both GDM+ and GDM- children [32]. Results from these two studies show inconsistencies and illustrate that more research in this area is needed to better understand the role of BM composition on obesity prevention in this population.

Mechanisms

As presented above, BM composition can vary according to several factors, including maternal diabetes status [35] and the type of maternal diabetes during the breastfeeding period can affect differently BM composition [35], highlighting the importance to analyze women with previous GDM as a distinct population than women with pre-existing diabetes. Indeed, the fact that maternal glycemia generally returns to normal range within few weeks after delivery in most GDM women may explain differences in BM composition between these two distinct populations [36]. This may also explain why results presented in this review suggested that breastfeeding is not associated with an increased risk of obesity but rather tended to be associated with a protective effect, like it is observed in the general population. However, the longer duration of breastfeeding needed in some studies to prevent childhood obesity suggest that longer duration of breastfeeding is necessary in this population given their higher risk of obesity.

Finally, disparities in results presented in this review can be explained by many factors, mainly the use of various breastfeeding measures across studies. Indeed, many authors categorized breastfeeding into groups of different durations or exclusivity, which may limit the interpretation of its effect on growth. On the other hand, analysing the duration of exclusive breastfeeding as a continuous variable or using a validated score to assess intensity of breastfeeding seemed more appropriate to better understand the association between breastfeeding and infant growth. Furthermore, the variety of anthropometric measurements taken at different stages of life also contributed to the heterogeneity of results between studies.

Quality of the evidence

Among studies showing a negative association between breastfeeding and obesity-related outcomes in childhood or adolescence, those conducted by Sauder et al. [30] and Vandyousefi et al. [31] were prospective cohort studies that obtained a strong rating in the quality assessment process, suggesting results of great quality to support the association between breastfeeding and reduced obesity risk. On the other hand, the important number of studies conducted in childhood or adolescence that obtained a weak rating [10-12, 22, 29] as well as several studies showing no association [13, 22, 23, 26] highlighted the need to conduct more prospective cohort studies of strong quality. For the infancy period, it should be noted that majority of studies were of moderate quality, and the only study of strong quality showed no association between breastfeeding and obesity-related outcome in infancy [26].

Conclusion

This review highlighted that breastfeeding is generally associated with a better anthropometric profile among GDM+ children, mainly during childhood and adolescence, but that additional studies of strong quality are needed to confirm this finding. More mechanistic studies are needed to understand these associations. Nevertheless, breastfeeding is associated with many other health benefits for both the mother and her child and should therefore always be encouraged in this population.

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Tables

Table 4. 1 Characteristics and main results of included studies

Authors and year	Aim	Study Design	Study Population	GDM diagnosis criteria	BF measure	Obesity related outcomes	Children's age at outcome measurement	Main findings	Quality
Aris et al. 2017[13]	To investigate the association between breastmilk intake and growth among GDM+ and GDM- children	Cohort study	N= 1016 GDM+: 181 GDM-: 835	WHO	No BF, BF<4 and ≥4 milk months for any type of BF (including partial BF)	Age-gender SDS for BMI and weight, weight gain	Birth, 3, 6, 9, 12, 15, 18, 24 and 36 months	BF ≥4 months associated with higher weight gain and BMI SDS in the first 6 months of life among GDM+ children. However, higher BM intake is associated with decelerate growth in the first 36 months of life in GDM- but not in GDM+ children.	Moderate
Dugas et al. 2021[23]	To investigate the association between total and exclusive BF duration and weight-for-age z-score trajectory from birth to 5 years among GDM+ and GDM− children	Cross-sectional study	N=166 GDM+: 103 GDM-: 63	Diabetes Canada	Exclusive and total BF duration	Weight-for-age z-score trajectory	Birth to 5 years	Total and exclusive BF durations were not associated with weight-for-age z-score trajectory from birth to 5 years among GDM+ and GDM− children.	Moderate

Dugas et al. 2018[22]	To investigate the association between early life nutrition, including BF duration, on anthropometric profile of GDM+ children	Cross-sectional study	GDM+: 104	Diabetes Canada	Exclusive and total BF duration	Age-gender weight z-score and BMI z-score, waist circumference and fat mass percentage	2 to 14 years	Total and exclusive BF duration were not associated with weight z-score, BMI z-score, waist circumference and fat mass percentage of GDM+ children.	Weak
Fenger-Grøn et al. 2015[25]	To evaluate growth, feeding patterns and their associations during the first 5 months of life among GDM+ children	Cohort study	GDM+: 131	Danish guideline	Exclusivity (fully breastfed/ partly breastfed/ no breastfed) and BF duration before 5 months	BMI SDS and weight gain	Birth to 5 months	BF associated with lower BMI at 5 weeks and lower weight and BMI at 5 months of age among GDM+ children.	Moderate
Gunder-son et al. 2018[9]	To evaluate the relation between feeding methods and infant growth among GDM+ children	Cohort study	GDM+: 464	Carpen-ter and Coustan	Calculation of a BF score: minimum of 0 (exclusively formula feeding); maximum of 12 (exclusive BF for 12 months).	Weight-for-age (WAZ) and weight-for-length (WLZ) z-scores, skin-fold thicknesses	Birth to 12 months	High intensity and longer duration of BF in the first year of life among GDM+ children may slow WAZ and WLZ trajectory compared to formula-fed infants.	Moderate
Hui et al. 2018[26]	To examine the association between exposure to GDM and adiposity from infancy to	Cohort study	N=7297 GDM+: 539 GDM: 6758	Self-reported	Feeding in the first 3 months categorized as: always formula-fed, mixed feeding or always BF.	BMI z-score	Infancy (3-9 months), childhood (2-<8 years) and adolescence (8-16 years)	No clear effect of exclusive BF during the first 3 months of life on BMI z score in infancy, childhood, and	Strong

	adolescence, and whether the association differ by mode of feeding in early life							adolescence among GDM+ children.	
Kaul et al. 2019[27]	To investigate the association of maternal diabetes, large for gestational age and BF with overweight or obesity in pre-school-aged children	Cohort study	N= 81 226 GDM+: 5136 GDM-: 75 432 Pre-existing diabetes (T1D or T2D): 658	Medical records	If no BF in the last 7 days at the 2- or 4-months visit = not being BF group; Otherwise = BF prior to 5 months group.	Overweight or obese status according to WHO criteria for children aged between 5-19 years	4 to 6 years	BF prior 5 months is associated with overweight/obesity risk reduction in GDM+ that were AGA but not among those that were LGA.	Moderate
Kramer et al. 2014[28]	To characterize the antepartum determinants of rapid weight gain in the first 3 months of life in a cohort of GDM+ and GDM- infants	Cohort study	N= 340 GDM+: 90 GDM: 250	National diabetes Data Group criteria	Duration of exclusive BF	Normal weight gain (<0.5 SDS) or rapid weight gain (≥0.5 SDS)	Birth to 3 months	Exclusive BF duration is positively associated with weight gain in the first 3 months of life in GDM- but not in GDM+ children.	Moderate
Rode-kamp et al. 2005[29]	To investigated whether diabetic BM intake during the late neonatal period and early infancy influences risk of overweight and diabetes in GDM+ children	Cohort study	N= 112 GDM+: 29 Pre-existing diabetes (T1D): 83	Fuhrman criteria	During first week of life: mean volume of milk ingested per day. BF at follow-up visits: BF only or no BF during 2-4 weeks of life.	Relative body weight (RBW) to children's age and sex.	2 years	Diabetic BM intake in the first week of life is associated with higher RBW at 2 years among GDM+ children. BF status at 2-4 weeks is not associated with RBW at 2 years when adjustment	Weak

								for BM intake in the first week of life is made (entire sample).	
Sauder et al. 2019[30]	To examine the association of exposure to GDM with body size and adiposity in childhood and adolescence among offspring with optimal versus suboptimal lifestyle habits	Cohort study	N= 939 GDM+: 147 GDM: 792	National Diabetes Data Group	Calculation of BM month using exclusivity score. ≥6 BM months (optimal) vs <6 BM months (suboptimal).	BMI, waist-to-height ratio, and subscapular-to-triceps skinfold ratio	6 to 19 years	Among suboptimal BF, GDM+ children had higher BMI, visceral and subcutaneous adipose tissues, and skinfold ratio than GDM- children. However, among optimal BF, only subcutaneous adipose tissue and skinfold ratio were higher among GDM+ children.	Strong
Schaeffer Graf et al. 2006[10]	To assess the association between BF during infancy and the prevalence of overweight in early life among GDM+ children	Cross sectional study	GDM+: 324	German criteria	Exclusive BF ≤3 months vs >3 months.	Childhood overweight defined as BMI ≥90th percentile	2 to 8 years	Exclusive BF >3 months is associated with lower risk of overweight in childhood among GDM+ children.	Weak
Shearrer et al. 2014[11]	To examine the relationship between maternal GDM status and BF duration on the prevalence of	Cross sectional study	N= 2287 GDM+: 232 GDM: 2055	Self-reported	No BF, BF <3 months, BF 3 to <6 months, BF 6 to <12months and BF≥12 months	Overweight if BMI-for-age <85th percentile and obese if BMI for- age < 95th percentile	2 to 4 years	BF ≥12 months is necessary to reduce obesity risk among GDM+ children compared to any	Weak

	overweight and obesity in the offspring							duration among GDM- children.	
Vandyou-sefi et al. 2021[31]	To evaluate the independent and joint associations between BF measures and infant dietary intake and child BMI percentile categories at 2–5 years of age among GDM+ children	Cohort study	GDM+: 835	Carpen-ter and Coustan	Exclusive and total BF ≥6 months vs <6 months. Calculation of a BF score: minimum of 0 (exclusively formula feeding); maximum of 12 (exclusive BF for 12 months).	Overweight if BMI ≥85th to <95th percentile and obese if BMI ≥95th percentile	2 to 5 years	Any BF <6 months, exclusive BF <6 months and BF score <6 were associated with higher risk of obesity at 2-5 years among GDM+ children.	Strong
Vandyou-sefi et al. 2019[12]	To examine the individual and interaction effects of exclusive BF, sugar-sweetened beverages intake and GDM status on obesity prevalence	Cross sectional study	N= 3707 GDM+: 470 GDM: 3237	Self-reported	Exclusive BF ≥6 months vs <6 months	1 to 2 years: high weight-for-length if ≥97.7th percentile. 2 to 5 years: obese if BMI for age ≥95th percentile or overweight if BMI for age ≥85th percentile.	1 to 5 years	Exclusive BF ≥6 months is associated with a reduce risk of obesity among GDM+ children aged between 1 and 5 years.	Weak
BM compo-sition									
Fatima et al. 2018[24]	To investigate levels of irisin and SREBP-1c in mature BM of GDM+ and	Cohort study	N= 66 GDM+: 33 GDM-: 33	IADPSG	Collection of colostrum (within 72 hours of birth) and mature	Weight at birth and 6 weeks	Birth to 6 weeks	GDM+ women have lower levels of irisin in their colostrum and mature BM and	Moderate

	GDM- women and their association with weight gain in infants				milk (at 6 weeks post-partum)			irisin levels positively associated with weight at 6 weeks in the entire sample.	
Yu et al. 2018[32]	To evaluate hormone concentrations in BM of GDM+ and GDM- women and the relationship with infant growth	Cohort study	N= 96 women GDM+: 48 GDM-: 48	Carpen-ter and Coustan	BM collection at 3 days (colostrum), 42 and 90 days (mature milk)	Weight-for-height	3 months	Lower level of adiponectin in BM of GDM+ women and adiponectin is associated with lower weight-for-age in GDM+ and GDM- children.	Strong

GDM: gestational diabetes mellitus, GDM+: exposed to GDM, GDM-: unexposed to GDM. BF: breastfeeding, WHO: World Health Organization, SDS: standard deviation score, BMI: Body mass index, WAZ: weight-for-age z score, WLZ: weight-for-length z score, T1D: type 1 diabetes, T2D: type 2 diabetes, IADPSG: International Association of the Diabetes and Pregnancy Study Group, AGA: adequate for gestational age, LGA: large for gestational age, RBW: relative body weight.

Table 4. 2 Association between breastfeeding and anthropometric profile among GDM+ children

References	Positive association	Negative association	No association	Quality
Infancy (<2 years)				
Aris et al. 2017 [13]	•			Moderate
Dugas et al. 2021 [23]			•	Moderate
Fenger-Grøn et al. 2015 [25]		•		Moderate
Gunderson et al. 2018 [9]		•		Moderate
Hui et al. 2018 [26]			•	Strong
Kramer et al. 2014 [28]			•	Moderate
Vandyousefi et al. 2019 [12]		•		Weak
Childhood and adolescence (2-18 years)				
Aris et al. 2017 [13]			•	Moderate
Dugas et al. 2021 [23]			•	Moderate
Dugas et al. 2018 [22]			•	Weak
Hui et al. 2018 [26]			•	Strong
Kaul et al. 2019 [27]		•		Moderate
Rodekamp et al. 2005 [29]	•			Weak
Sauder et al. 2019 [30]		•		Strong
Schaeffer-Graf et al.2006 [10]		•		Weak
Shearrer et al. 2014 [11]		•		Weak
Vandyousefi et al. 2021 [31]		•		Strong
Vandyousefi et al. 2019 [12]		•		Weak

Figures

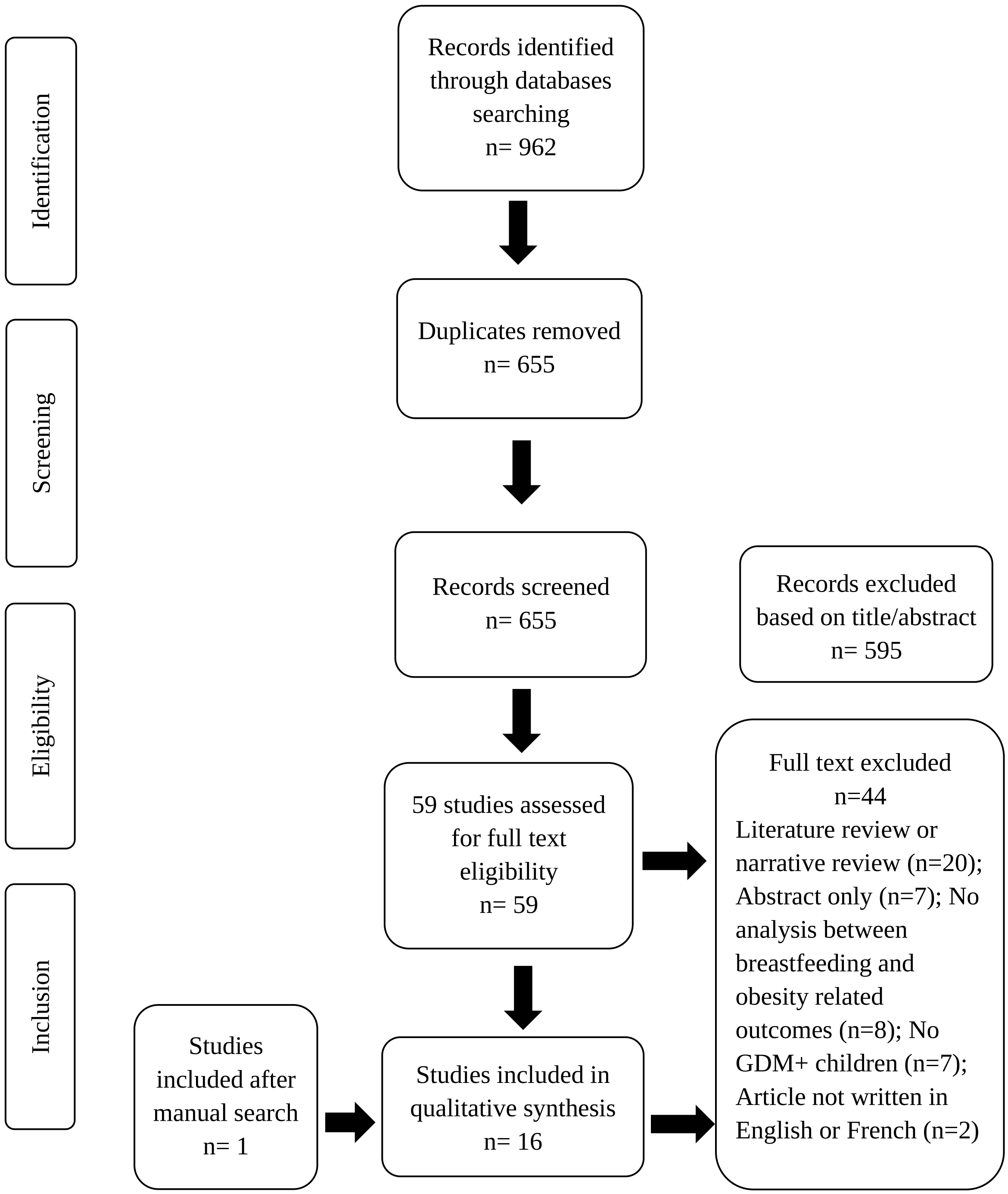

Figure 4. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart showing selection of the studies included in the present systematic review

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Chapitre 5 Allaitement et courbes de croissance de 0 à 5 ans chez des enfants exposés et non exposés au diabète gestationnel

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L'article présenté dans ce chapitre s'intitule: *Breastfeeding and growth trajectory from birth to 5 years among children exposed and unexposed to gestational diabetes mellitus in utero*

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Résumé

Objectifs: Cette étude vise à évaluer l'association entre l'exposition au diabète gestationnel (DG) *in utero* et la courbe de croissance de la naissance à cinq ans et d'évaluer si l'allaitement maternel influence cette association selon le statut d'exposition au DG.

Méthodes: Le poids à 0, 6, 12, et 18 mois et 2, 3, 4, et 5 ans a été recueilli de façon rétrospective chez 103 enfants exposés et 63 enfants non-exposés au DG. Les scores Z du poids pour l'âge ont été calculés. Des modèles linéaires mixtes pour mesures répétées ont été utilisés pour tester si l'allaitement maternel était associé différemment à la courbe du score Z du poids pour l'âge selon le statut d'exposition au DG.

Résultats: Les enfants exposés au DG avaient un score Z du poids pour l'âge plus grand à 6 mois, 4 et 5 ans ($p<0.10$). La durée de l'allaitement maternel n'était pas associée avec la trajectoire du score Z du poids pour l'âge dans les deux groupes d'enfants.

Conclusion: Les enfants exposés au DG ont une courbe de croissance différente en début de vie, mais la durée de l'allaitement maternel ne semble pas influencer cette association.

Abstract

Objectives: This study aims to evaluate the association between exposure to gestational diabetes mellitus and growth trajectory from birth to 5 years and to test whether breastfeeding influences this association among children exposed and unexposed to gestational diabetes.

Study Design: Weight at 0, 6, 12, 18 months and 2, 3, 4, 5 years were retrospectively collected for 103 children exposed and 63 children unexposed to gestational diabetes. Weight-for-age z-score were calculated. Mixed linear model for repeated measurements were computed to test whether breastfeeding was associated differently with weight-for-age z-score of children exposed or unexposed to diabetes.

Results: Children exposed to gestational diabetes had greater z-score values at 6 months, 4 and 5 years ($p<0.10$). Breastfeeding duration was not associated with weight-for-age z-score trajectory in any children.

Conclusion: Children exposed to gestational diabetes had a different growth trajectory in early life, but breastfeeding duration did not seem to influence this association.

Title Page

Breastfeeding and growth trajectory from birth to 5 years among children exposed and unexposed to gestational diabetes mellitus *in utero*

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Short title: Gestational diabetes, breastfeeding, and growth

Introduction

Despite efforts made to prevent its development, obesity remains highly prevalent worldwide among children[1]. Although adopting healthy lifestyle habits have known benefits on body weight [2], other factors influence obesity risk, such as in utero development and early life nutrition [3, 4]. In fact, in utero exposure to gestational diabetes mellitus (GDM), defined as hyperglycemia diagnosed or recognized for the first time during pregnancy [5], is associated with a risk of increased fetal growth, higher birth weight and obesity later in life [6-8]. While many studies assessed the association between GDM and obesity risk, only few studies investigated growth curves from birth to early childhood among children exposed (GDM+) and unexposed (GDM-) to GDM [9, 10] and, to our knowledge, none of them were conducted in a Canadian population.

Infancy is a critical period for development and early life nutrition plays an important role in health programming [11]. Many studies showed that babies breastfed for longer duration had different growth trajectory than those breastfed less longer or fed with infant formula, mainly due to the unique composition of breast milk [12-14], and that slower growth of breastfed infants would protect them from obesity later in life [15]. Given the high risk of obesity among GDM+ children, it is thus relevant to investigate the role of breastfeeding on their growth trajectory but results from previous studies are inconsistent [16-18]. Indeed, Gunderson et al. showed that high intensity breastfeeding during the first year of life was associated with lower weight gain in this period in GDM+ children [16]. Crume et al. also found that breastfeeding for ≥6 months was associated with slower growth trajectory during infancy and childhood in children born from mothers with GDM or pre-existing diabetes [17]. On the other hand, Aris et al. showed that among Asian GDM+ children, breastfeeding for ≥4 months was associated with greater weight gain and body mass index (BMI) in the first 6 months of life, while it was associated with lower weight gain among GDM- children [18]. Thus, conflicting results found in the very few studies on this topic highlighted the need for further investigations. Furthermore, these previous studies used a breastfeeding score, based on the intensity of breastfeeding for a specific duration, generally limited to the first 12 months of life. This limits the interpretation of the results given that different types of breastfeeding (exclusive and non-exclusive) are grouped together. In addition, no study assessed the association between breastfeeding duration and growth trajectory after 36 months of life among GDM+ children only, i.e. not exposed to other type of diabetes. Accordingly, this study aims to 1) compare weight-for-age z-score trajectory from birth to 5 years between GDM+ and GDM- children and 2) investigate the association between total and exclusive breastfeeding duration and weight-for-age z-score trajectory from birth to 5 years among GDM+ and GDM- children.

Methods

Study Population

Children and mother dyads were recruited in a retrospective cohort study conducted at the Institute of Nutrition and Functional Foods (INAF), Université Laval (Quebec city, Canada), that aimed to evaluate the impact of GDM on children's and mother's health and to investigate strategies to prevent these complications. The project has been previously described [19]. Briefly, GDM+ and GDM- children born between 2003 and 2013 and their mother were recruited. Recruitment has been conducted using medical records from the two major hospitals with a neonatal care unit in the area of Quebec City (*Hôpital Saint-François d'Assise* and *Centre Hospitalier de l'Université Laval*), using data from the provincial health plan registry (*Régie de l'Assurance Maladie du Québec*), emails to the Université Laval community and publicity posted on health care websites and on social medias. GDM+ children had to be born from women with GDM only, i.e. no pre-existing diabetes. Children from the control group (GDM-) had to be born from a mother that never had any type of diabetes (GDM, type 1 or type 2 diabetes). In addition to participants of this cohort study, mothers with and without prior GDM and their children aged between 3 and 12 years were later recruited through emails sent to the Université Laval community and were also included in this analysis. This last group of women completed online questionnaires only and no onsite visit was required. GDM diagnosis during pregnancy was confirmed for 90% of women participating in the cohort study and was obtained either from the medical record or the provincial health plan registry and GDM status was self-reported for other participants. Majority of children included (92.8%) were born before 2013, i.e. when GDM was diagnosed with 2003 criteria of Diabetes Canada [20]. Consent was obtained from mothers for both mother and children and ethical approval was obtained from the *Université Laval* Ethics Committee (2011-196-A-4 R-3) and from the *Centre Hospitalier Universitaire de Québec* Ethics Committee (2015-2031) for both project, i.e. the cohort study and the online phase. This cohort study was registered in the Clinical Trials.gov registry (NCT01340924).

Outcomes

For all children, weight from birth to the age attained at the time of the study were retrospectively collected using the child health record, a tool used in Canada by pediatrician and health care professionals to document growth and health during the first years of life. The number of weight measurements as well as the timing of the data collection varied between children. Thus, only weight at ages 0, 6, 12 and 18 months and 2, 3, 4 and 5 years were used in this study. Furthermore, only children with ≥2 weight measurements were included. Among included children, 9% had only 2 weight measurements available, with the majority having between 5 and 7 measurements (57.2%) and 13% of them having all the 8 weight measurements. Weight-for-age z-scores were calculated using the SAS Macro Igrowup developed by the World Health Organization (WHO) [21]. Z-scores express the weight value as a number of standard deviations above or below the reference mean or median value for a specific age group and sex. A change in weight-for-age z-score of >0.67 unit for the first year or the first two years of life were defined as a rapid weight gain (RWG) [22, 23]. Finally, birth weight z-score was calculated using United States national reference standard for size at birth according to gestational age[24].

Data collection

All mothers of children included in this study completed self-administered questionnaires, at the time of the visit at the research center, i.e. when the child was between 2 and 14 years, regarding infant feeding practices during infancy and antenatal data. These retrospective data were collected to determine if the child had ever been breastfed during infancy and the duration of total and exclusive breastfeeding (in months and/or weeks), if applicable. Exclusive breastfeeding was defined as the period when the infant was fed with breast milk only, i.e. no other liquid or solid food [25]. Total breastfeeding was defined as any type of breastfeeding, i.e. including exclusive and non-exclusive breastfeeding for those receiving infant formula or any food or liquid in addition to breast milk. Data about whether breast milk was expressed or directly from the breast were not available. Maternal age and gestational age were collected. For mothers with previous GDM, the use (yes or no) and the type of medication (insulin or oral hypoglycemic agent) were also documented.

For mothers participating in the cohort study, anthropometric measurements were assessed during the visit at the research center, i.e. 2 to 14 years post-partum. Weight was measured to the nearest 0.1 kilogram with a calibrated balance (Tanita BC-418) and height was measured to the nearest 0.1 centimeter using a stadiometer. For mothers recruited subsequently for the online phase, current body weight and height at the time of the study, which was the same time frame than women in the cohort study, were self reported. Current maternal BMI was calculated for all mothers (kg/m^2).

Statistical analyses

Participant characteristics were compared between GDM+ and GDM- groups using student T-test, Chi-square test (χ^2) or Fisher exact test. Prevalence of RWG among GDM+ and GDM- were compared using χ^2. Weight-for-age z-score trajectories were modeled using mixed linear model for repeated measurements, which allows for incomplete data if they are missing at random. Socio-demographic characteristics and breastfeeding status were compared between children with ≤4 weight measurements available (n=50) and those with >4 measurements (n=116) and no differences were observed, which validate that data were missing at random. First, weight-for-age z-score trajectories were compared between GDM+ and GDM- children. Afterward, mixed linear model for repeated measurements were computed to test whether total or exclusive breastfeeding duration was associated differently with growth among GDM+ and GDM- children. Covariance structures were determined according to Akaike's Information Criteria (AIC). Adjustment for gestational age and children's sex were made in all models. Additional adjustments for birth weight, current maternal BMI, maternal age, family income and maternal education level were also tested. Assumptions for statistical analysis were tested and data transformation according to Box-Cox procedure was computed when needed. Analyses of the present study were not pre-registered and are considered exploratory, explaining why no a priori power calculations were computed. The statistical software SAS studio was used to compute analyses.

Results

A total of 166 children (n=103 GDM+ and n=63 GDM-) aged between 2 and 14 years were included in these analyses. Children recruited subsequently in the online phase (n=35, n=6 GDM+ and n=29 GDM-) did not differ from those of the cohort study (n=131, n=97 GDM+ and n=34 GDM-) regarding birth weight, gestational age, exclusive breastfeeding duration and family income (Supplementary Table 1). However, there was a higher proportion of mothers with a university degree (88.6% compared to 62.1%, p=0.01) and a higher proportion of boys (68.6% compared to 48.9%, p=0.04) in the group of children recruited for the online phase compared to children from the cohort study, respectively (Supplementary Table 1). Finally, mothers from the cohort study were slightly older, had higher BMI at the time of the study and breastfed for a shorter duration (non-exclusively) than mothers from the online phase (Supplementary Table 1).

Mothers from the control group (GDM-) were more educated, younger at delivery, had lower BMI at the time of the data collection and breastfed their child for a longer duration than mothers with prior GDM (Table 1). As shown in Table 2, GDM+ children were born earlier but had similar birth weight than GDM- children even after adjustment for gestational age. Birth weight z-score were also similar between groups (Table 2). Prevalence of RWG during the first year and the first two years of life was similar in GDM+ and GDM- children (Table 2).

However, weight-for-age z-score trajectory from birth to 5 years differed between GDM+ and GDM- children (Figure 1). Particularly, GDM+ children had greater z-score values at 6 months (0.31±1.08 compared to -0.05±1.31 for GDM-, p=0.04, CI: 0.01-0.80), 4 years (0.54±1.16 compared to 0.09±0.92 for GDM-, p=0.04, CI: 0.02-0.79) and 5 years of age (0.38±1.00 compared to 0.00±0.83 for GDM-, p=0.07, CI: -0.02-0.67). After adjustment for birth weight, current maternal BMI, maternal age, family income and maternal education level, results remained similar (p for interaction GDM status x time = 0.03) although differences between GDM+ and GDM- children at specific ages were no longer observed (p>0.10 for each specific age). More specifically, the mean difference in weight-for-age z-score between GDM+ and GDM- children at every age are presented in Table 3. In addition, we observed that a weight-for-age z-score loss of 0.1 unit between 0 and 6 months was observed in the GDM- group while GDM+ children gained 0.23 unit of weight-for-age z-score during this period (Figure 1).

Total breastfeeding duration was not associated differently with weight-for-age z-score among GDM+ and GDM- children, after adjustment for infant sex and gestational age (p for interaction = 0.36). This result remained similar after additional adjustment for birth weight, current maternal BMI, maternal age, family income and maternal education level (p=0.44). Furthermore, there was no association between exclusive breastfeeding duration and weight-for-age z-score according to GDM status (p for interaction = 0.89, adjusted for infant sex and gestational age). Additional adjustments for birth weight, current maternal BMI, maternal age, family income and maternal education level did not change this result (p for interaction = 0.67). Estimates regression parameters are presented in Table 4.

Discussion

This study showed that in utero exposure to GDM is associated with different weight-for-age z-score trajectory from birth to 5 years. Particularly, GDM+ children had higher weight-for-age z-scores at 6 months, 4 and 5 years of age compared to GDM- children despite similar birth weight z-score, although these differences were no longer observed after adjustment for sociodemographic characteristics. In addition, GDM- children presented a period of catch-down growth between birth and 6 months that was not observed among GDM+ children. On the other hand, the prevalence of RWG in infancy, a predictor of childhood obesity, was similar between groups. Finally, neither total nor exclusive breastfeeding duration were associated with weight-for-age z-score trajectory in GDM+ or GDM- children. These results are of great importance to better understand the impact of GDM exposure on infant growth and the role of the postnatal period in obesity prevention among these high-risk children.

First, results of this study highlight for the first time, within a French-Canadian cohort, that weight-for-age z-score trajectory from birth to 5 years differed between GDM+ and GDM- children. The present study also showed that prevalence of RWG for the first year and the first two years of life was similar between GDM+ and GDM- children. These results are in accordance with results from a prospective cohort study conducted by Hu et al. among Americans showing that being exposed to GDM increased the relative risk (RR) of childhood obesity at 4 years of age but did not increase the RR of having a rapid BMI gain in the first year of life, followed by a stable high BMI until 4 years [9]. Furthermore, results from the Exploring Perinatal Outcomes among Children (EPOCH) study, a retrospective cohort study that included children aged between 6 and 13 years, showed that children exposed to pre-existing diabetes or GDM during pregnancy had higher BMI growth trajectory from 27 months to 13 years when compared to children unexposed to any type of diabetes during pregnancy, while early life BMI trajectory (from birth to 26 months) was not different between groups [10]. These results partly support findings of the present study, suggesting that differences in growth between children exposed and unexposed in utero to GDM would be observed in early childhood, after the first two years of life. Hui et al. also found, in a Chinese birth cohort study, that exposure to GDM in utero was associated with higher BMI z-score during childhood (2-8 years) and adolescence (8-16 years) [26]. However, authors also found an inverse association between GDM exposition and BMI z-score in infancy (3 and 9 months), which is not in agreement with result from this study [26]. Although the exact timing of anthropometric alterations in GDM+ children is still unclear, results from these previous studies highlighted that the negative impact of diabetes exposure on children's body weight would appear in early childhood and not as early as infancy, i.e. the first 2 years of life. We also previously showed that adiposity was increased in GDM+ children compared to GDM- children at ages 3-12 years, which would suggest an altered anthropometric profile during childhood resulting from an in utero exposure to GDM, even when BMI is not altered [27]. Further studies should evaluate adiposity longitudinally, from birth to childhood, in this specific population in order to better understand the impact of GDM exposure on obesity development.

Mechanisms explaining the different weight-for-age z-score trajectory observed among children exposed to in utero GDM are not fully understood. It has been suggested that high glucose levels during pregnancy would enhance fetal growth, resulting in higher birth weight, which predisposes infants to obesity later in life [8]. However, in the present study, birth weight and birth weight z-scores were similar between GDM+ and GDM- suggesting an adequate glycemic control during pregnancy for these women. Indeed, although glycemic profile during pregnancy was not available in the current study, Morisset et al. showed that women with GDM receiving dietetic counseling at the CHU de Québec (same hospital than the current study) reduced carbohydrate intake and had adequate gestational weight gain during pregnancy compared to the control group, which resulted in similar birth weight between GDM+ and GDM- newborns [28]. Furthermore, it has been shown by Landon et al. that GDM treatment with diet counseling and use of insulin therapy, if needed, is effective for fetal growth reduction and resulted in normal birth weight in these children [29]. On the other hand, it is also possible that despite similar birth weight, fat mass accumulation and distribution could differ between groups. Indeed, Catalano et al. showed that GDM+ infant had increased body fat at birth compared to GDM- infant, even if birth weight was normal [30]. Another plausible explanation for the difference in growth curves observed in this study is epigenetic alterations caused by the in utero exposure to diabetes that could predispose children to future diseases, including obesity [31]. However, it is also possible that maternal obesity could be in part responsible for the association between GDM exposure and differences observed in the growth trajectory in the offspring. Indeed, several studies showed that the association between GDM and children's body weight is attenuated when results are adjusted for maternal obesity [32]. This could be a result of an altered fetal environment in the context of maternal obesity, a genetic predisposition to obesity or the impact of sharing an obesogenic environment with the child after birth [33, 34]. On the other hand, given that obesity is a risk factor for GDM [35], one can argue on whether adjusting for this variable would be an over-adjustment because a part of the pathology would be ruled out of the association tested.

Secondly, a period of catch-down growth was observed between birth and 6 months among GDM- children, while GDM+ children followed a positive linear growth from birth to 1 year of age. This finding is not in accordance with results from previous studies showing a period of catch-down growth after birth in offspring of diabetic mothers [36, 37]. Results from these previous studies are in line with plausible mechanisms suggesting that higher birth weight, generally caused by inadequate maternal glucose levels during pregnancy and fetal hyperinsulinism, would result in a period of catch-down growth after birth [38]. However, no difference in birth weight and birth weight z-score were observed between GDM+ and GDM- children in the present study. Thus, further studies should be conducted in a larger population to confirm this finding.

Thirdly, breastfeeding duration (either total or exclusive) was not associated with growth trajectory of GDM+ and GDM- children. These results agree with a previous study conducted by our research team showing no association between breastfeeding duration in infancy and anthropometric profile at the mean age of 6 years among GDM+ children [39]. Furthermore, the present results are in accordance with another study showing that breastfeeding status (i.e. only formula-fed, mixed-fed or exclusively breastfed) in the first 3 months of life was not associated with BMI z-score of either GDM+ or GDM- children from infancy to adolescence (p for interaction >0.4) [26]. Furthermore, results from the present study partly agree with Aris et al. who found, in a prospective cohort study conducted in an Asian population, no significant interaction between age and breastmilk intake on weight standard deviation score (SDS) among GDM+ children [18]. However, this latter study showed that greater breast milk intake was associated with higher SDS weight gain in the first 6 months of life only among GDM+ children, while it was inversely associated with SDS weight gain among GDM- children between 6 and 12 months [18]. On the other hand, results presented here are not in agreement with results from the EPOCH study that showed that being breastfed ≥6 months was associated with a reduced growth velocity in childhood, particularly between 4 and 9 years of age, in both children exposed and unexposed to diabetes during pregnancy [40]. In the same line, results from the SWIFT Offspring study showed that high intensity breastfeeding from birth to 9-12 months was associated with lower increase in weight-for-age z-score in GDM+ infants during the first year of life, when compared to infants exclusively or mostly formula-fed [16]. Thus, literature is still conflicting regarding the impact of breastfeeding on children's growth among GDM+ children.

It has been suggested by Plagemann et al. that breast milk composition of women with diabetes or prior GDM could be altered, explaining results of their study showing that consumption of human milk from women with diabetes in the first week of life was associated with increased body weight at 2 years of age, while being fed with human milk from non-diabetic women (from a bank of donors) was inversely associated with body weight at follow-up [41]. Indeed, some studies showed that breast milk content in glucose, lipids and hormones involved in appetite regulation and energy metabolism, such as ghrelin, would be altered in the context of diabetes or GDM [42-46]. As previously highlighted by our group [47], breast milk composition would be altered mainly when glycemic control is not adequate during the breastfeeding period, suggesting that alterations would be only transitory for women with GDM, given that glycemia generally returns to normal ranges for these women few weeks after delivery [42]. Thus, given that blood samples at the time of breastfeeding were not available in this study, it is possible that the majority of GDM mothers had adequate glycemic control during most of their breastfeeding period, resulting in normal breast milk composition, which could explain the lack of differences found in this study. In fact, this hypothesis is likely given that according to Feig et al., the probability of developing type 2 diabetes in the first 9 months postpartum among women with previous GDM was only 3.7%, while it increases to 19% after 9 years [48]. Furthermore, it has been hypothesized that GDM+ children should be breastfed for a longer duration than GDM- children to observe a protective effect of breastfeeding against obesity development [47]. It is possible that a longer duration of breastfeeding would have produced different results. Thus, the fact that current studies in the literature use different definitions of adequate and inadequate breastfeeding duration makes it difficult to compare results between studies and could explain the lack of consensus on whether breastfeeding affects growth of GDM+ children or not. In the present study, breastfeeding duration was analyzed as a continuous variable, both for total and exclusive breastfeeding, which limits the comparison with studies using different cut-offs of adequate or inadequate breastfeeding. However, studying the exclusive breastfeeding period is of major interest given that exclusive breastfeeding represents a diet entirely composed of breast milk, which removes potential bias of other liquids or solids consumed by the infant that could affect growth. On the other hand, analysis of total breastfeeding duration did not include quantity or frequency of milk consumed, which limits interpretation of these results. Further analyses should be conducted in a larger population in order to better understand the role of breastfeeding in the association between GDM status and early life growth.

This study had some limitations. First, given the retrospective study design, only weight measurements from the child health record were used to assess growth trajectory over time. However, these measures can be considered relatively reliable given that they are performed as part of a systematic follow-up by healthcare professionals such as pediatricians, nurses or physicians. On the other hand, data on height of children, allowing calculation of BMI z-score, and fat mass measurements would allow better assessment of infant's growth. This study is also at risk of recall bias regarding breastfeeding data collection, although it has been demonstrated that maternal recall for breastfeeding information is reliable up to 20 years after the breastfeeding period [49]. Furthermore, as mentioned above, it is possible that the lack of association between breastfeeding and children's growth observed in this study was due to a lack of statistical power, given the small number of participants. In addition, all weight measures were not available for each participant although the statistical model used in this analysis considers unbalanced data. Furthermore, dietary intakes and physical activity level of children were not available, which could have an influence on children's growth, particularly after weaning and in early childhood. Other factors such has parents' lifestyle and health could also have had an impact on results observed and were not considered in this study. Particularly, as mentioned above, maternal BMI during pregnancy could potentially attenuate the association between GDM and children's growth[32, 50]. In this study, maternal BMI during pregnancy was not available but additional adjustment for current maternal BMI led to similar results. Another limitation of the study is the fact that two cohorts with some differences in baseline characteristics and data assessment (maternal BMI) were combined in analyses. Finally, these results cannot be generalized to other population. Indeed, similar birth weight z-scores between groups suggest adequate glycemic control among GDM mothers, which could differ from other women with GDM. On the other hand, this study also had many strengths. First, only few studies have evaluated weight trajectory from birth to early childhood among GDM+ children and to our knowledge, none of them was conducted in a Canadian population. The inclusion of 8 weights measurements collected by health professionals, from birth to 5 years, is also a strength because it offers an insight into early life as well as early childhood growth patterns. Furthermore, the use of WHO z-score was also a strength as it considers children's body weight for their specific age and sex relative to the general population, which represents a reliable indicator of children's growth. Potential cofactors of the association between GDM exposure, breastfeeding and growth have been considered in analyses, such as maternal health and social determinants of health, which is also a strength of this study. Moreover, as mentioned above, one particularity of this study is the analysis of exclusive breastfeeding duration as a continuous variable, which remove potential bias of other food and liquid consumed by the infant during the breastfeeding period that could affect its growth. Finally, only women with previous GDM, i.e. no other type of diabetes, were included in this study, which is of major importance given that different types of diabetes can modulate differently children's health.

In conclusion, results of the present study showed that GDM+ children had a different weight-for-age z-score trajectory from birth to 5 years, particularly with higher weight-for-age z-scores at 6 months, 4 and 5 years of age. Total and exclusive breastfeeding durations did not seem to influence this association. These results are of great interest to better understand the impact of in utero exposure to GDM on early life growth and the role of breastfeeding in this association. However, further studies should be conducted in a larger sample to confirm these results. Finally, breastfeeding should always be encouraged, particularly among GDM+ women, given proven benefits of breastfeeding on mother and child health.

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Conflicts of interest

Authors have no conflict of interest to disclose.

Authors contributions

SJW, IM and JR participated in the conception and the design of the study. CD, MK, and JP made a substantial contribution to data acquisition. CD and JR participated in data analysis and interpretation. CD wrote the first draft of the manuscript. All authors revised it critically for important intellectual content and approved the final version. JR is responsible of the integrity of the study.

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Supplementary information is available at JPER's website.

Tables

Table 5. 1 Participant's characteristics

Characteristics	Mean ± SD or n (%)		
	GDM+ n= 103	**GDM- n= 63**	**p value**
Demographic			
Sex			
Boys	53 (51.5)	35 (55.6)	0.61
Girls	50 (48.5)	28 (44.4)	
Family income (CAD$/year)			
0 – 39 000	9 (10.7)	10 (17.5)	0.05
40 000 – 79 000	26 (31.0)	10 (17.5)	
80 000- 99 999	22 (26.2)	9 (15.8)	
>100 000	27 (32.1)	28 (49.1)	
Maternal education level			
High school or less	17 (18.5)	4 (6.8)	**0.02**
College	20 (21.7)	7 (11.9)	
University	55 (59.8)	48 (81.4)	
Maternal age at delivery (years)	32.2±4.1	29.6±4.1	**0.0001**
Current maternal BMI (kg/m^2)	26.9±6.9	23.5±3.9	**0.0001**
GDM treatment (insulin or oral therapy)	56 (54.9)	-	-
Infant feeding			
Breastfed infant	88 (87.1)	58 (93.6)	0.19
Total breastfeeding duration (months)	8.8±7.5	12.3±9.1	**0.004**
Exclusive breastfeeding duration (months)	4.2±1.8	4.9±1.5	**0.03**

Results are mean ± standard deviation or n (%) and were compared using Student t-test, chi-square test or Fisher exact test. GDM: gestational diabetes mellitus.

Table 5. 2 Anthropometric data at birth and during infancy

		Mean ± SD or n (%)		
		GDM+	**GDM-**	**p value**
Size at birth				
Gestational age (weeks)		38.8±1.2	39.3±1.3	**0.03**
Birth weight (kg)		3.35±0.47	3.34±0.53	0.92*
Birth weight z-score		-0.06±0.93	-0.21±1.03	0.31**
Weight gain during infancy				
0-1 year				
	NWG	49 (57.0)	30 (62.5)	0.53
	RWG	37 (43.0)	18 (37.5)	
0-2 years				
	NWG	36 (62.1)	15 (45.5)	0.12
	RWG	22 (37.9)	18 (54.5)	

GDM+: exposed to gestational diabetes mellitus, GDM-: unexposed to gestational diabetes mellitus, NWG: normal weight gain (change in weight-for-age-z-score ≤0.67), RWG: rapid weight gain (change in weight-for-age-z-score >0.67). *Adjusted for gestational age. ** Adjusted for infant sex.

Table 5. 3 Weight-for-age z-score mean difference between children exposed and unexposed to gestational diabetes mellitus in utero

	Model 1				Model 2			
Age	**Mean difference**	**Confidence interval**		**P value**	**Mean difference**	**Confidence interval**		**P value**
0	0.13	-0.18	0.43	0.420	0.01	-0.03	0.04	0.746
6 months	0.41	0.01	0.80	0.042	0.36	-0.08	0.81	0.110
12 months	0.21	-0.12	0.54	0.212	0.11	-0.26	0.48	0.544
18 months	0.07	-0.28	0.41	0.701	0.04	-0.34	0.42	0.840
2 years	0.07	-0.29	0.43	0.708	-0.04	-0.44	0.37	0.860
3 years	0.08	-0.28	0.44	0.657	-0.03	-0.44	0.38	0.882
4 years	0.40	0.02	0.79	0.040	0.34	-0.10	0.77	0.129
5 years	0.32	-0.02	0.67	0.068	0.13	-0.31	0.56	0.567

Model 1: adjustment for gestational age and infant sex. Model 2: Model 1 with additional adjustment for maternal education level, family income, maternal age, maternal body mass index and birth weight.

Table 5. 4 Estimates regression parameters for mixed linear model for interaction of gestational diabetes mellitus exposure and breastfeeding duration on weight-for-age z-score over time

	Total breastfeeding duration		**Exclusive breastfeeding duration**	
Effect	**Estimation**	**Pr > |t|**	**Estimation**	**Pr > |t|**
Intercept	-3.35	0.10	-2.02	0.37
GDM status	-0.01	0.95	-0.39	0.35
Time 0	-0.45	0.03	0.08	0.84
Time 1	-0.08	0.70	0.25	0.54
Time 2	0.24	0.16	0.45	0.14
Time 3	0.29	0.07	0.40	0.16
Time 4	0.25	0.12	0.25	0.38
Time 5	0.0007	0.99	0.08	0.78
Time 6	-0.10	0.51	0.07	0.77
Breastfeeding	-0.02	0.15	-0.04	0.62
Breastfeeding*GDM status 1*time 0	0.04	0.09	0.05	0.69
Breastfeeding*GDM status 1*time 1	0.02	0.44	0.05	0.70
Breastfeeding*GDM status 1*time 2	0.02	0.40	0.07	0.49
Breastfeeding*GDM status 1*time 3	0.02	0.36	0.10	0.31
Breastfeeding*GDM status 1*time 4	0.02	0.33	0.11	0.27
Breastfeeding*GDM status 1*time 5	0.03	0.19	0.12	0.25
Breastfeeding*GDM status 1*time 6	0.04	0.11	0.10	0.32
Breastfeeding*GDM status 1*time 7	0.03	0.11	0.14	0.10
Breastfeeding*GDM status 2*time 0	0.03	0.08	-0.05	0.59
Breastfeeding*GDM status 2*time 1	-0.003	0.86	-0.10	0.27
Breastfeeding*GDM status 2*time 2	0.005	0.75	-0.04	0.53
Breastfeeding*GDM status 2*time 3	0.01	0.53	-0.01	0.84
Breastfeeding*GDM status 2*time 4	0.01	0.32	0.03	0.66
Breastfeeding*GDM status 2*time 5	0.01	0.41	0.004	0.95
Breastfeeding*GDM status 2*time 6	0.006	0.69	-0.03	0.60
enf_sex	0.24	0.06	0.31	0.02
gest_age	0.09	0.07	0.06	0.30

Models are adjusted for infant sex and gestational age. N=143 for total breastfeeding duration and N=121 for exclusive breastfeeding duration. GDM status 1= children exposed to gestational diabetes mellitus, GDM status

2= children unexposed to gestational diabetes mellitus. Time 0= birth, time 1= 6 months, time 2= 12 months, time 3= 18 months, time 4= 2 years, time 5= 3 years, time 6= 4 years and time 7= 5 years. Beta coefficient that included reference value (beta= 0) are not presented.

Supplementary Table 5. 1 Characteristics of children recruited in the cohort study and in the online phase

Characteristics	Mean ± SD or n (%)		
	Children from the cohort study n= 131	**Children from the online phase n= 35**	**p value**
Demographic			
Exposed to gestational diabetes (yes)	97 (74.1)	6 (17.1)	**<.0001**
Sex			
Boys	64 (48.9)	24 (68.6)	**0.04**
Girls	67 (51.1)	11 (31.4)	
Gestational age (weeks)	39.0±1.2	39.0±1.4	0.91
Birth weight (kg)	3.34±0.47	3.38±0.55	0.63
Family income (CAD$/year)			
0 – 39 000	15 (14.0)	4 (11.8)	0.12
40 000 – 79 000	31 (29.0)	5 (14.7)	
80 000- 99 999	25 (23.4)	6 (17.7)	
>100 000	36 (33.6)	19 (34.6)	
Maternal education level			
High school or less	20 (17.2)	1 (2.9)	**0.01**
College	24 (20.7)	3 (8.6)	
University	72 (62.1)	31 (88.6)	
Maternal age at delivery (years)	31.5±4.5	30.0±3.4	0.07
Maternal BMI (kg/m^2)	26.1±6.3	23.9±5.4	0.06
Infant feeding			
Breastfed infant	115 (89.2)	31 (91)	0.73
Total breastfeeding duration (months)	9.42±7.35	13.1±10.8	0.08
Exclusive breastfeeding duration (months)	4.42±1.74	4.9±1.57	0.20

Results are mean ± standard deviation or n (%) and were compared using Student t-test, chi-square test or Fisher exact test. BMI: body mass index.

Figures

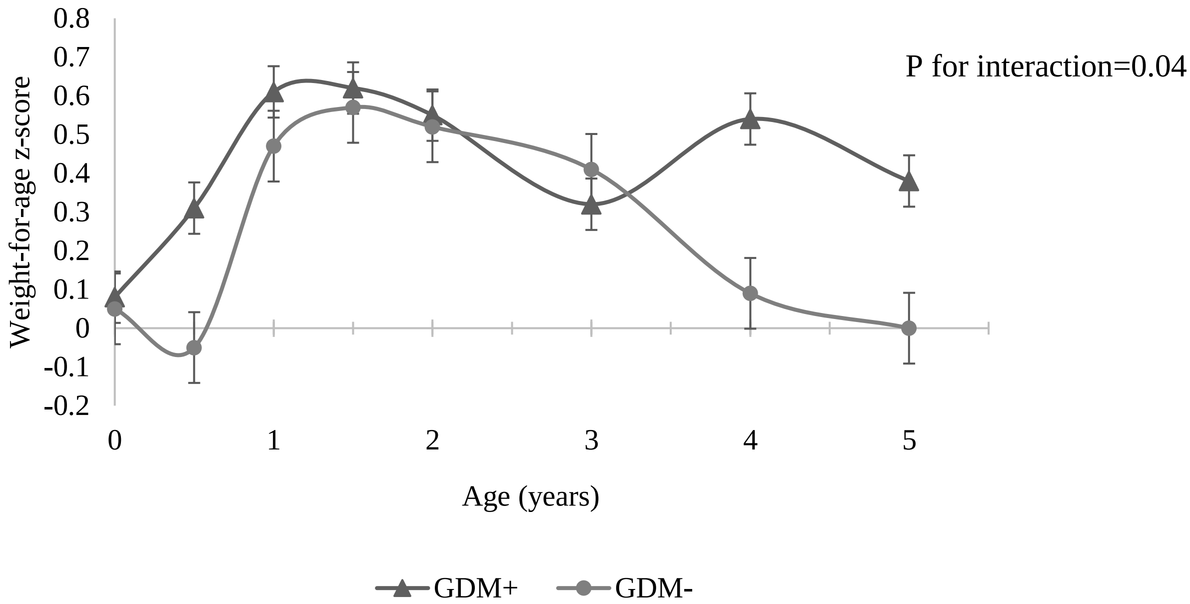

Figure 5. 1 Weight-for-age z-score trajectory according to in utero exposure to GDM

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Chapitre 6 Association entre le diabète gestationnel, la composition du lait en macronutriments et la croissance chez le nourrisson

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Résumé

Le diabète gestationnel (DG) est connu pour affecter la composition du lait maternel (LM). Les objectifs de cette étude étaient de comparer le contenu en macronutriments du LM de femmes avec (DG+) et sans (DG-) antécédent de DG, et d'évaluer l'association entre la composition du lait et la croissance des enfants. Deux mois après l'accouchement, des échantillons de LM de fin de tétée ont été collectés. Les concentrations de triglycérides (TG), lactose, protéines et énergie ont été mesurées dans ces échantillons. Un test de tolérance au glucose a été réalisé. Le poids et la taille des enfants à la naissance et deux mois ont été collectés dans le carnet de santé. Le score Z du poids pour l'âge (WAZ) et le score Z du poids pour la taille (WLZ) ont été calculés. Un total de 24 femmes DG+ et 29 DG- âgées de 33,5 ±3,6 et 30,0 ±3,1 ans, respectivement, ont été recrutées. Les niveaux de protéines, lactose et énergie étaient similaires dans le LM des deux groupes alors que la concentration de TG était plus élevée dans le lait des femmes DG+ (6,3 ± 2,0 vs. 5,3 ± 1,2, p=0,04). Les résultats étaient atténués après ajustements pour l'âge de la femme et le sexe de l'enfant (p=0,23). L'âge de la mère était associé aux niveaux de TG (r=0,28, p=0,04) et de lactose (r=-0,30, p=0,03), alors que la glycémie à jeun était associée aux protéines (r=0,30, p=0,03) et tendait à être associée aux TG (r=0,27, p=0,05) et à l'énergie (r=0,24, p=0,08). Les niveaux de TG du LM étaient associés au poids (ß: 0,22, 95%CI: 0,06-0,38), WAZ (ß: 0,34, 95%CI: 0,11-0,58) et WLZ (ß:0,42, 95%CI: 0,12-0,73) à deux mois chez les enfants DG-, mais pas chez les DG+. Pour conclure, le statut de DG, l'âge de la mère et son profil glycémique sont associés à la composition du LM. Finalement, les TG du LM sont associés avec la croissance des enfants DG- mais pas celle des enfants DG+.

Abstract

Gestational diabetes mellitus (GDM) is known to affect human milk (HM) composition. Aims of this study were to compare macronutrients content of HM of women with (GDM+) and without GDM (GDM−) and to assess their association with infant growth. Two months after delivery, hindmilk samples were collected. Triglyceride (TG), lactose, and protein content of HM was measured. An oral glucose tolerance test was performed. Infant weight and height at birth and two months were collected. Weight-for-age (WAZ) and weight-for-length (WLZ) z-scores were calculated. A total of 24 GDM+ and 29 GDM− women aged of 33.5 ±3.6 and 30.0 ±3.1 years, respectively, were included. Protein, lactose, and energy content of HM was similar between groups while TG concentration was higher in GDM+ than in GDM− women (6.3 ± 2.0 vs. 5.3 ± 1.2, p=0.04). This difference was no longer significant after adjustment for maternal age and infant sex (p=0.23). Maternal age was associated with TG (r=0.28, p=0.04) and lactose (r=-0.30, p=0.03), while fasting glucose was associated with proteins (r=0.30, p=0.03) and tended to be associated with TG (r=0.27, p=0.05) and energy (r=0.24, p=0.08). TG levels in HM were associated with weight (ß: 0.22, 95%CI: 0.06-0.38), WAZ (ß: 0.34, 95%CI: 0.11-0.58) and WLZ (ß:0.42, 95%CI: 0.12-0.73) at two months among GDM− children, but not among GDM+ children. In conclusion, GDM status, maternal age and fasting glucose and insulin levels were associated with HM composition. Finally, TG in HM was associated with infant growth among GDM− children but not among GDM+ children.

Title page

Association between gestational diabetes mellitus, macronutrients content of human milk and infant growth

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Introduction

Gestational diabetes mellitus (GDM), defined as hyperglycemia with first onset or recognition during pregnancy[1], is a complication of pregnancy that is widely prevalent, affecting one in sixth births worldwide.[2] From 1989 to 2012, its prevalence raised from 2.5% to 7.6% in the Province of Quebec, in Canada.[3] This increased prevalence is also observed worldwide, and might reflect or contribute to the epidemic of obesity and type 2 diabetes observed in developed countries for the past decades.[4] Indeed, GDM is associated with later consequences for both the mother and her offspring.[5, 6] Among others, mothers and children are at risk of developing type 2 diabetes[7-9], and women with prior GDM (GDM+ women) are encouraged to be screened for diabetes within the first six weeks to six months after delivery.[10] In utero exposure to GDM is also associated with an increased risk of obesity.[11]

Increasing evidence suggests that the early postnatal period could be a critical window of opportunity to intervene among high-risk individuals, and nutrition during this period could play a key role in this long-term fetal programming.[12] Indeed, human milk represents the ideal food for infants in the first six months of life and has been associated with a reduced risk of obesity compared to formula feeding.[13] Human milk feeding has been shown to be associated with obesity prevention among GDM+ children, although a longer duration of human milk feeding seems necessary to achieve the protective effect of human milk in this population.[14] Moreover, some studies rather showed that human milk feeding was associated with increased obesity-related outcomes among GDM+ children, and authors of these studies suggested that this could be due to an altered composition of human milk in the context of diabetes.[15-17]

In this regards, a recent review of the literature showed that human milk composition of GDM+ women is altered in different components such as insulin, ghrelin, or leptin, as well as in macronutrients.[18] However, among the few studies that investigated the association between GDM status and macronutrients content of mature human milk, results are conflicting.[19-21] Given that these components of human milk are known to influence infant growth, studying the association between human milk macronutrients content in the context of GDM and infant growth is relevant to find mechanisms linking the association between breastfeeding and growth in this population at high risk of obesity.[22] In addition, the role of maternal anthropometric and glycemic profiles in the association between GDM status and human milk composition has not been previously investigated. Indeed, obesity, a known risk factor for GDM, as also been shown to alter the human milk composition.[23]

Accordingly, aims of this study were, at two months postpartum: 1) to compare human milk content in triglycerides (TG), lactose, proteins, and energy of GDM+ women with women without GDM (GDM− women), 2) to evaluate the association between maternal anthropometric and glycemic profiles and macronutrients composition of human milk, and 3) to evaluate the association between human milk composition in macronutrients and infant's growth from birth to two months of age. We hypothesized that human milk composition is different between groups, that maternal health profile is associated with the human milk composition, and that human milk composition is associated with infant's growth, regardless of the GDM status of the mother.

Methods

Participants

Women with a pregnancy complicated by GDM and followed by endocrinologists and dieticians at the two main hospitals with a neonatal care unit in Quebec City, Canada, were invited to participate in a clinical trial starting two months after delivery that aimed at achieving healthy lifestyle habits to prevent development of type 2 diabetes (clinical trial NCT02872402). Invitations to participate in this study were also sent by emails to the community of Université Laval. The recruitment ended in September 2019. This study included GDM+ women, aged older than 18 years with a BMI greater than 18.5 kg/m^2. Women with multiple pregnancy were excluded, as well as those who gave birth to a preterm baby (< 37 weeks), women with type 1 or type 2 diabetes mellitus, those who have had a bariatric surgery, and those who were planning a pregnancy for the next year. Women from a control group (GDM− women) were recruited from March 2020 to September 2020 using emails from the Université Laval community as well as posts shared on social medias. The same inclusion and exclusion criteria than GDM+ women were applied, except that these women did not have any history of GDM. Written consent was provided by all participants and both studies were approved by the *Centre Hospitalier Universitaire de Québec* Ethics Committee (2017-3225 and 2020-5075).

Data collection

GDM+ women participated in an intervention study for 18 months, starting at two months postpartum (Trottier C et al. unpublished). For the current study, only data collected during the baseline visit (at two months postpartum) were used. GDM− women were submitted to the same baseline visit than GDM+ women. During this visit, all participating women completed a self-administered sociodemographic questionnaire as well as questionnaires on infant feeding practices and antenatal data.

Maternal metabolic profile

During the visit at the research center, weight of all women was measured on a calibrated balance to the nearest 0.1 kg, height was measured using a stadiometer, and BMI was calculated (kg/m^2). Body composition was measured with a dual energy X-ray absorptiometry scanner (DXA, GE Lunar Prodigy Bone Densitometer, GE Healthcare Lunar, Madison, WI, USA) by trained professionals using the Lunar enCORE software version 14.1 and body fat distribution (fat mass percentage and fat mass percentage in android and gynoid regions) was analyzed as previously described.[24] Fasting blood sample was collected for all women and a 75g 2-hours oral glucose tolerance test (OGTT) was performed. Plasma glucose and insulin at 0 and 2-hour were measured enzymatically and using radioimmunoassay, respectively.[25, 26] The homeostasis model assessment for insulin resistance (HOMA-IR) index was calculated as following: (fasting insulinemia (μU/L)*fasting glycaemia (mmol/L)/22.5).[27]

Infant growth

Weight and height at birth and at two months of age were collected using the child health record, a tool used in Canada by pediatrician and health care professionals to document growth and health during the first years of life. Weight-for-age (WAZ) and weight-for-length (WLZ) z-scores were calculated using the growth standard charts from the World Health Organization (WHO) developed for girls and boys.[28, 29] The difference in growth parameters between two months and birth was calculated and presented as delta (Δ) values.

Human milk collection

Women were asked to provide 30 to 60 mL of hindmilk during the visit or at home at the closest moment from the 2-month visit. Human milk was either pumped or expressed manually and was collected in a sterile cup. The exact timing of the human milk collection was documented by the mother and samples were categorized based on the timing of collection i.e., morning (6:00 to 11:59 am), afternoon (12:00 to 17:59 pm), evening (18:00 to 23h59 pm) and night (12:00 to 5:59 am). All human milk samples were stored in freezers at -20°C for one month after collection, and at -80C° afterwards. Frozen samples were defrosted at 0 to 4°C and were vigorously stirred before aliquoted in 2 mL samples. Another freezing cycle at -80°C was performed for all samples prior laboratory analysis.

Human milk assay

TG content of human milk was measured by colorimetry (Single Reagent, GPO PAP Method, 2018). Given that TG represents 98% of lipids in human milk[30], it was used as a surrogate for total lipids content of human milk. Similarly, lactose represents the main carbohydrate of human milk and was then used as a surrogate for carbohydrates.[31, 32] Lactose was measured by high-performance liquid chromatography (HPLC) with a Agilent 1100 chromatograph (Agilent Technologies, Santa Clara, CA, USA), equipped with an Agilent 1260 refractive index detector (RID). An ICSep ICE-ION-300 column (Transgenomic, Omaha, Nebraska, USA) was used with 0.0065N of H2SO4 as the mobile phase, at a flow rate of 0.4 mL/min and the run time is 45 minutes. The column temperature was kept constant at 40°C. Samples were diluted by 2 in acetonitrile, and the supernatant was then diluted by five-fold dilution with ultra pure water, and filtered (nylon 0.45 µm; Chromatographic Specialties, Brockville, ON, Canada) before injection (15 µL). A mixture of standards: lactose, glucose, and galactose (all from Sigma-Aldrich) was used as an external standard. Total solids were analyzed according to the AOAC international method (990.20, 2000). Total protein content of dried human milk was determined by the Dumas combustion method using a Rapid Micro N Cube (Elementar, Francfort-sur-le-Main, Germany). Nitrogen content was converted into a protein concentration by applying a nitrogen-to-protein conversion factor of 6.25.[33] All samples were analyzed in duplicate, and concentrations were converted in g/100 mL of human milk. Energy content of human milk was calculated using Atwater conversion where 9, 4 and 4 kilocalories (kcal) are associated to every gram of lipid, carbohydrate, and protein, respectively.[34]

Statistical analyses

Participant's characteristics were compared using Student t test, Chi-square test (χ^2) or Fisher exact test. Human milk composition between GDM+ and GDM− women was compared using Student t test (model 1) and ANOVA adjusted for maternal age and infant sex (model

2). Pearson's coefficients of correlation were calculated to assess the association between maternal characteristics and human milk composition in the entire cohort and separately among GDM+ and GDM− groups. Finally, multivariable regression models were computed to estimate the potential association between macronutrient content of human milk and infant anthropometric profile at birth, two months and between birth and two months. Interactions with GDM status were tested in these models to verify whether human milk composition association with growth varies according to in utero exposure to GDM. Models were adjusted for maternal BMI, gestational age, and infant sex. The statistical software SAS version 9.4 was used to compute analyses. Post-hoc power calculation using G*power software (version 3.1.9.7, 2020) was computed using current sample size and parameter estimates derived from the comparison of TG levels between groups and a statistical power of 69% was obtained.

Results

Participant's characteristics are presented in Table 1. Briefly, GDM+ women were older than the control group, had higher pre-pregnancy and current BMI, total fat mass percentage and fat mass percentage in gynoid and android regions, as well as higher values of plasma glucose and insulin (**Table 1**). None of the participating women, either from GDM+ or GDM− groups, were diabetic at the time of the visit. The proportion of boys among offspring in the GDM+ group was higher than among GDM− women (**Table 1**).

Human milk content in protein, lactose and energy was similar between GDM+ and GDM− women, while the TG concentration in human milk of GDM+ women was higher than in the control group (6.28 ± 2.03 g/100 mL compared to 5.29 ± 1.18 g/100 mL, p=0.04, respectively, **Table 2**). This difference was no longer significant after adjustments for maternal age and infant sex (**Table 2**).

As shown in **Table 3**, maternal fasting glucose was positively associated with concentrations of proteins, TG, and energy while fasting insulin was associated with energy content of human milk in the entire cohort. On the other hand, when analyses were conducted separately, fasting insulin levels and HOMA-IR were positively associated with protein, TG, and energy content of human milk among GDM+ women only. Finally, maternal age was negatively associated with lactose concentrations in human milk in the entire cohort only, and positively associated with TG levels in human milk of all women and among GDM− women. Additional adjustment for the timing of human milk collection and infant sex did not change results observed (results not shown).

Finally, associations between human milk composition and infant growth are presented in **Table 4**. In the entire cohort, every increase of 1 g of lactose per 100 mL of human milk was associated with an increase in 0.38 unit of change in WLZ between birth and two months of age. In the same line, every increase of 1 kcal per 100 mL of human milk was associated with an increase of 0.02 units of WLZ at two months in all children.

Some human milk components were associated with growth parameters at two months differently according to children *in utero* exposure to GDM, as shown by a test for interaction between human milk composition and GDM status that revealed some incompatibility with the null hypothesis of no interaction (p values <0.05, **Table 4**). Indeed, TG levels in human milk were positively associated with weight (ß: 0.22, 95%CI: 0.06 - 0.38), WAZ (ß: 0.34, 95%CI: 0.11 - 0.58) and WLZ (ß: 0.42, 95%CI: 0.12 - 0.73) at two months among GDM− children, while no association was seen among GDM+ children (ß: -0.03, 95%CI: -0.39 - 0.32; ß:-0.06, 95%CI: -0.58 - 0.47 and ß: -0.07, 95%CI: -0.74 - 0.60, respectively). Furthermore, proteins and energy levels in human milk were associated differently with WLZ among GDM+ and GDM− children (p for interaction of 0.02 and 0.001, respectively, **Table 4**). Proteins levels were associated positively with WLZ among GDM− children (ß: 1.82, 95%CI: 0.24 - 3.41) while the association was not significant among GDM+ children (ß: -0.85, 95%CI: -4.63 - 2.92). Finally, energy in human milk was positively associated with WLZ among GDM− children and negatively associated among GDM+ children (ß: 0.05, 95%CI: 0.02 - 0.08 and -0.007, 95%CI: 0.12 - 0.05, respectively).

Discussion

Results of this study showed that GDM+ women had higher levels of TG in their mature human milk compared to the control group. However, this association may be partly explained by their more advanced age. Other factors such as fasting glucose and insulin levels were also associated with human milk composition, although in a different manner between GDM− and GDM+ mothers, highlighting the importance to monitor glycemia during the postpartum period. Finally, TG levels in human milk, a surrogate measure of the lipid content of human milk, was positively associated with infant's weight, WAZ and WLZ at two months in GDM− but not in GDM+ children.

Human milk concentrations in lactose, proteins and energy were similar between GDM+ and GDM− women, while concentration in TG was higher among GDM+ women. However, this difference was no longer significant after adjustment for maternal age and infant sex. The study conducted by Dritsakou et al. showed no difference in lipid concentration between human milk of GDM+ and GDM− women.[20] Nevertheless, they found that human milk of GDM+ women contained higher energy levels, and they hypothesized that this could be due to a higher lipid content in human milk of GDM+ women that was not statistically perceived in their results.[20] On the other hand, results of the present study are not in accordance with the study conducted by Shapira et al. that instead observed lower lipid concentration in human milk of GDM+ compared to GDM− women.[19] However, this latter study collected human milk samples only two weeks after delivery, compared to two months in the current study, which could explain difference in results.[19] Furthermore, adjustments for important cofactors, such as maternal age, were not performed in these previous two studies.[19, 20]

In the present study, maternal age was associated with human milk composition, particularly with lactose and TG content in all women. This result is in accordance with results from Dritsakou et al. that observed a positive association between maternal age and fat content of mature human milk[20], and with other studies conducted in transitory milk or colostrum. [35-37] This association may be explained by the fact that older women - older age being a risk factor for GDM - would produce less amount of milk, given that a lower density of mammary glands and hormonal changes occur with age, resulting in a different human milk composition.[36, 38]

However, it has also been proposed that human milk lipid production is greater among older women compared to younger women.[37] Further investigations should be conducted to better understand why the association between maternal age and lipid content of human milk was only seen among GDM− women, when analyses were conducted separately in both groups, as well as involved mechanisms.

This study also showed that fasting glucose levels were associated with protein, lipid, and energy content of human milk in all women, while fasting insulin was positively associated with energy. Furthermore, among GDM+ women only, fasting insulin and HOMA-IR were associated with protein, TG, and energy content of human milk. To our knowledge, no other study has evaluated the association between the glycemic and insulinemic profile of GDM+ women at the time of human milk collection and the nutritional composition. However, other studies conducted among women with type 1 diabetes suggested that the underlying hypothesis behind differences in human milk composition of women with and without diabetes is partly based on glucose dysregulation associated with this pathology. Accordingly, results conducted among type 1 diabetic lactating women showed that when diabetes is tightly controlled, macronutrients content in human milk is not different than in the general population.[39] Further studies are needed to better understand the role of maternal glycemic profile during the breastfeeding period on human milk composition.

This study also showed that human milk composition in TG was associated differently with weight, WAZ and WLZ at two months according to in utero exposure to GDM, and these results were independent of maternal BMI. Our results may prompt that the presence of certain macronutrients in human milk would be associated differently with infant's growth depending on GDM status of the mother, particularly the TG concentration of human milk, which is in turn associated with the mother's higher insulin. On the other hand, the positive association between the TG content of human milk and weight parameters among GDM− children is in contradiction with results from Prentice et al. showing a negative association between TG in human milk and infant growth.[40] However, this negative association was observed between 3 and 12 months, while there was no association observed at 3 months of age.[40] Furthermore, the current study did not evaluate the lipid composition of human milk, i.e. the proportion of different lipid components, which may also affect infant growth and could possibly explain the differences observed with results from other studies.[22] To our knowledge, no study investigated the association between macronutrients content in human milk and infant growth among GDM+ children specifically, which makes it difficult to compare results of the present study with others. Nonetheless, it is possible to speculate that the association between human milk feeding and infant growth among GDM+ children may be of lower magnitude than among GDM− children, given their predisposition to obesity.[14] It is also possible that the absence of association observed among GDM+ children is a result of a lack of statistical power, given the lower number of participants with weight measurements in this group. Thus, further analyses conducted among a larger group of GDM+ children are needed to confirm results of the current study.

Finally, the positive association observed between lactose, the main carbohydrate of human milk, and infant growth in the entire sample is in accordance with other studies conducted in the general population.[40, 41] Prentice et al. hypothesized that greater intakes of carbohydrates would result in greater storage of glycogen and fat, explaining the positive association with infant weight measurements.[40]

This study presented several strengths. First, in addition to assessing the association between GDM status and human milk composition in macronutrients, the link between human milk composition and infant growth has been investigated, answering a gap of the current literature. Second, anthropometric and glycemic profiles of women were assessed at the same moment that human milk samples were collected, allowing the investigation of the association between maternal health and human milk composition in the context of GDM. Finally, human milk samples were collected and analyzed using a standardized protocol to ensure comparability of samples between groups. On the other hand, limits of this study included the fact that human milk samples were collected only once. Indeed, pooled milk samples collected during 24h would have been more representative of the real composition of human milk ingested by the breastfed infant. Moreover, this study did not document the quantity of human milk consumed by the infant. Furthermore, multiple cycles of freezing may have affected stability of human milk samples in this study although as mentioned above, the same method was used for all samples to ensure that this did not affect comparisons between groups. Finally, results of this study could not be generalized to other populations than Caucasian women with a high degree of education. Also, the mean BMI of participants in both groups were relatively high, and GDM+ women had normal glycemic profile with none of them having type 2 diabetes at the time of the visit.

To conclude, this study suggested that some risk factors for GDM, such as advanced maternal age, may explain the association between GDM status and higher levels of TG in human milk. Although maternal age is not a modifiable factor, other factors such as glycemia and insulinemia were also associated with human milk composition, highlighting the importance to control glycemia during the postpartum period among GDM+ women. This study also suggested that lipids in human milk were associated with infant weight parameters at two months of age in a different manner between GDM+ and GDM- children. While further studies are needed in a larger sample of women, this study suggests that maternal characteristics such as GDM status, advanced age or fasting glycemia and insulinemia may affect the composition of human milk and therefore, affect infant growth. This strengthened the need to better understand the impact of maternal health, including GDM status, on human milk composition as well as on the future health of infants.

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Conflict of interest

None

Tables

Table 6. 1 Participant's characteristics

Characteristics	Total sample n= 53	GDM+ n= 24	GDM− n= 29	P value*
Demographic				
Age (years)	31.6 ± 3.7	33.5 ± 3.6	30.0 ± 3.1	<0.001
Parity (number of children)				
1	28 (2.8)	12 (50.0)	16 (55.2)	0.71
2 or more	25 (47.2)	12 (50.0)	13 (44.8)	
Gestational age at birth (weeks)	39.1 ± 1.1	38.6 ± 1.0	39.4 ± 1.1	0.01
Infant sex				
Girls	23 (44.2)	6 (26.1)	17 (58.6)	0.02
Boys	29 (55.8)	17 (73.9)	12 (41.4)	
Education level				
High school or less	3 (5.7)	1 (4.2)	2 (6.9)	0.91
College	9 (17.0)	4 (16.7)	5 (17.2)	
University	41 (77.3)	19 (79.2)	22 (75.9)	
Family income (CAD$/year)				
0 – 39 000	1 (1.9)	0 (0.0)	1 (3.5)	0.39
40 000 – 79 000	11 (20.8)	7 (29.2)	4 (13.8)	
80 000- 99 999	12 (22.6)	4 (16.7)	8 (27.6)	
>100 000	29 (54.7)	13 (54.2)	16 (55.2)	
Metabolic				
Pre-pregnancy BMI (kg/m^2)	28.6 ± 7.4	30.9 ± 7.7	26.8 ± 6.8	0.05
Current BMI (kg/m^2)	29.2 ± 6.6	31.0 ± 7.2	27.7 ± 5.9	0.07
Fat mass (%)	40.2 ± 8.1	42.7 ± 6.8	38.0 ± 8.6	0.03
Fat mass android (%)	42.6 ± 11.3	46.5 ± 8.6	39.2 ± 12.4	0.02
Fat mass gynoid (%)	45.2 ± 7.9	47.5 ± 7.1	43.3 ± 8.2	0.05
Fasting glucose (mmol/mL)	4.9 ± 0.4	5.0 ± 0.4	4.8 ± 0.3	0.05
2-hour glucose (mmol/L)	5.6 ± 1.3	6.2 ± 1.5	5.1 ± 0.9	0.002
Fasting insulin (pmol/L)	50.3 ± 29.6	49.4 ± 20.5	51.0 ± 35.4	0.70
2-hour insulin (pmol/L)	253.1 ± 142.4	302.0 ± 171.9	215.1 ± 102.5	0.08
HOMA-IR	1.60 ± 0.98	1.60 ± 0.75	1.60 ± 1.15	0.58

GDM+: women with gestational diabetes mellitus. GDM−: women without gestational diabetes mellitus. BMI: Body mass index. HOMA-IR: homeostasis model assessment for insulin resistance. Results are mean ± standard deviation or n (%). *Student t test, chi square test or Fisher exact test between DG+ and DG- groups.

Table 6. 2 Human milk composition according to GDM status

Components	Total n= 53	GDM+ n= 24	GDM− n= 29	P value model 1	P value model 2
Proteins (g/100mL)	1.2 ± 0.3 (0.7 – 2.1)	1.3 ± 0.3 (0.8 – 2.1)	1.2 ± 0.2 (0.7 – 1.8)	0.36	0.75
TG (g/100 mL)	5.7 ± 1.7 (2.2 – 10.7)	6.3 ± 2.0 (2.2 – 10.7)	5.3 ± 1.2 (3.3 – 7.0)	0.04	0.23
Lactose (g/100 mL)	11.9 ± 1.7 (8.8 – 16.1)	11.5 ± 1.5 (8.8 – 14.8)	12.2 ± 1.9 (9.7 – 16.1)	0.15	0.90
Energy (Kcal/100 mL)	104 ± 15 (76 – 143)	108 ± 18 (76 – 143)	101 ± 13 (77 – 129)	0.13	0.27

GDM+: women with gestational diabetes mellitus. GDM−: women without gestational diabetes mellitus. TG: triglycerides. Results are expressed as mean ± standard deviation with (minimum – maximum values). Means are compared using a student t test (model 1) and using ANOVA adjusted for maternal age and infant sex (model 2).

Table 6. 3 Association between maternal profile and human milk composition

Maternal Characteristics	**Entire sample**		**GDM+**		**GDM−**	
	r	p	r	p	r	p
			Proteins			
Age	0.20	0.15	0.16	0.46	0.17	0.38
BMI	0.13	0.34	0.16	0.45	0.04	0.84
Fat mass (%)	0.16	0.25	0.16	0.44	0.11	0.58
Android fat mass (%)	0.11	0.44	0.14	0.51	0.03	0.90
Gynoid fat mass (%)	0.18	0.19	0.17	0.44	0.15	0.44
Fasting glucose	**0.30**	**0.03**	0.33	0.12	0.22	0.25
2-hour glucose	0.15	0.30	0.04	0.86	0.28	0.16
Fasting insulin	0.20	0.16	**0.50**	**0.02**	-0.02	0.94
2-hour insulin	0.22	0.14	0.13	0.58	0.29	0.14
HOMA-IR	0.15	0.31	**0.54**	**0.01**	-0.11	0.59
			Lactose			
Age	**-0.30**	**0.03**	-0.17	0.42	-0.30	0.11
BMI	-0.04	0.78	-0.05	0.83	0.05	0.79
Fat mass (%)	-0.03	0.85	-0.04	0.85	0.08	0.67
Android fat mass (%)	-0.04	0.79	-0.0006	0.98	0.05	0.78
Gynoid fat mass (%)	-0.03	0.85	-0.06	0.78	0.09	0.66
Fasting glucose	-0.10	0.48	-0.31	0.14	0.19	0.33
2-hour glucose	-0.15	0.29	0.12	0.61	-0.28	0.15
Fasting insulin	0.16	0.26	0.25	0.26	0.14	0.47
2-hour insulin	-0.03	0.84	0.05	0.82	-0.007	0.97
HOMA-IR	0.06	0.69	0.08	0.72	0.05	0.79
			Triglycerides			
Age	**0.28**	**0.04**	0.03	0.90	**0.40**	**0.03**
BMI	0.18	0.19	0.14	0.51	0.09	0.65
Fat mass (%)	0.14	0.32	0.05	0.82	0.07	0.72
Android fat mass (%)	0.18	0.21	0.06	0.78	0.13	0.50
Gynoid fat mass (%)	0.07	0.64	-0.04	0.87	0.004	0.98
Fasting glucose	**0.27**	**0.05**	0.28	0.19	0.09	0.65
2-hour glucose	-0.13	0.37	-0.32	0.14	-0.18	0.36
Fasting insulin	0.23	0.11	**0.37**	**0.09**	0.12	0.53
2-hour insulin	0.17	0.26	0.21	0.37	-0.05	0.79
HOMA-IR	0.17	0.23	**0.40**	**0.07**	0.03	0.86
			Energy			
Maternal age	0.15	0.27	-0.02	0.93	0.17	0.37
BMI	0.17	0.23	0.14	0.52	0.11	0.59
Fat mass (%)	0.14	0.34	0.05	0.82	0.12	0.56
Android fat mass (%)	0.16	0.25	0.07	0.75	0.14	0.47
Gynoid fat mass (%)	0.07	0.64	-0.05	0.83	0.07	0.74
Fasting glucose	**0.24**	**0.08**	0.20	0.35	0.20	0.30
2-hour glucose	-0.19	0.19	-0.29	0.19	-0.30	0.12
Fasting insulin	**0.31**	**0.03**	**0.50**	**0.02**	0.18	0.34
2-hour insulin	0.17	0.26	0.24	0.30	-0.03	0.89
HOMA-IR	0.20	0.15	**0.47**	**0.03**	0.05	0.80

GDM+: women with GDM. GDM−: women without GDM. BMI: body mass index. Results are Pearson coefficient of correlation (r).

Table 6. 4 Association between human milk composition at 2 months and infant growth

Growth parameters	*Proteins*			*Lactose*			*Triglycerides*			*Energy*		
	Beta	**95% CI**	*P interaction with GDM status*	**Beta**	**95% CI**	*P interaction with GDM status*	**Beta**	**95% CI**	*P interaction with GDM status*	**Beta**	**95% CI**	*P interaction with GDM status*
Weight at 2 months[1]	-0.05	-0.68, 0.58	0.05	-0.02	-0.12, 0.08	0.21	0.08	-0.02, 0.18	**0.01**	0.007	-0.004, 0.02	0.16
Δ Weight 0-2 months[1]	-0.16	-0.71, 0.40	0.17	0.04	-0.05, 0.12	0.24	0.02	-0.08, 0.11	0.07	0.003	-0.006, 0.01	0.16
WAZ at 2 months[1]	-0.07	-1.01, 0.87	0.05	-0.03	-0.17, 0.12	0.22	0.12	-0.03, 0.27	**0.008**	0.01	-0.005, 0.03	0.20
Δ WAZ 0-2 months[1]	-0.30	-1.20, 0.59	0.35	0.09	-0.05, 0.23	0.29	-0.02	-0.16, 0.13	0.15	0.002	-0.01, 0.02	0.23
WLZ at 2 months[2]	0.47	-0.70, 1.63	**0.02**	0.16	-0.01, 0.33	0.50	0.11	-0.07, 0.28	**0.009**	**0.02**	**0.0003, 0.04**	**0.001**
Δ WLZ 0-2 months[3]	0.27	-1.51, 2.05	0.36	**0.38**	**0.14, 0.62**	0.80	-0.10	-0.37, 0.17	0.74	0.007	-0.02, 0.04	0.34

Results are beta estimates from regression analyses with confidence interval (CI) of 95% conducted in the entire cohort. Adjustments for gestational age, infant sex, and maternal body mass index were performed. Interaction for gestational diabetes mellitus (GDM) status were tested. [1]n= 17 for GDM+ and n=26 for GDM−, [2]n= 17 for GDM+ and n=22 for GDM−, [3]n= 16 for GDM+ and n=21 for GDM-.

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Chapitre 7 Association entre le moment d'introduction des jus pendant la petite enfance et la consommation d'aliments et boissons aux goût sucré chez des enfants exposés et non exposés au diabète gestationnel

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L'article présenté dans ce chapitre s'intitule: *Association between early introduction of fruit juice during infancy and childhood consumption of sweet-tasting foods and beverages among children exposed and unexposed to gestational diabetes mellitus in utero*

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Résumé

Mise en contexte: Les enfants exposés au diabète gestationnel (DG) *in utero* sont à risque de développer de l'obésité. Considérant que les habitudes alimentaires sont généralement maintenues de la petite enfance jusqu'à l'enfance, l'objectif de cette étude était d'évaluer l'association entre le moment d'introduction des jus de fruit pendant la petite enfance et la consommation d'aliments et de boissons au goût sucré pendant l'enfance chez des enfants exposés (DG+) ou non-exposés (DG-) au DG.

Méthodes: Un total de 107 enfants DG+ et 59 DG- ont été inclus. Les données concernant le moment d'introduction des jus pendant la petite enfance ont été collectées de façon rétrospective chez 62 enfants DG+ et 32 DG-. Les apports alimentaires actuels de l'enfant ont été collectés à l'aide de deux rappels alimentaires de 24h. Les enfants ont été divisés en groupes selon l'âge médian d'introduction des jus de fruits (9 mois).

Résultats: L'âge moyen des enfants était 6,3 ± 2,6 et 7,6 ± 3,7 ans pour les enfants DG+ et DG-, respectivement ($p=0.08$). L'âge moyen d'introduction des jus de fruits était similaire entre les deux groupes ($p > 0.05$). Consommer >1 portion de jus de fruits par jour était 2,72 fois plus fréquent chez les enfants DG+ ayant été introduits aux jus <9 mois, comparativement aux enfants DG+ introduits ≥9 mois (IC 95%: 1,19–6,20). Cette association n'a pas été observée dans le groupe DG-. Le moment d'introduction des jus de fruits n'était pas associé à la consommation de sucreries, desserts ou boissons sucrées pendant l'enfance après ajustement pour l'âge de l'enfant dans les deux groupes.

Conclusion: Une introduction précoce des jus de fruits chez l'enfant est associée à une plus grande prévalence de consommation de plus d'une portion de jus de fruits par jour chez les enfants DG+.

Abstract

Background: Children exposed to gestational diabetes mellitus (GDM) in utero are at high-risk of obesity. Given that nutritional habits can track from infancy to childhood, the aim of this study was to evaluate the association between the timing of fruit juice introduction in infancy and later consumption of sweet-tasting foods and beverages among children exposed (GDM+) and unexposed (GDM-) to GDM.

Methods: A total of 107 GDM+ and 59 GDM- participated in the project. Data on the timing of fruit juice introduction during infancy were retrospectively collected for 62 GDM+ and 32 GDM- children. Current dietary intakes were collected with two 24-hour dietary recall questionnaires. Children were divided into groups according to the median timing of juice introduction (9 months).

Results: Mean age of children was 6.3 ± 2.6 and 7.6 ± 3.7 years for GDM+ and GDM- children, respectively ($p=0.08$). Mean age of fruit juice introduction was similar between groups ($p > 0.05$). Consuming>1 serving of fruit juice per day was 2.72 times more prevalent among GDM+ children introduced to fruit juice<9 months, compared to GDM+ children introduced ≥9 months (CI: 1.19–6.20). This association was not observed in the GDM- group. The timing of fruit juice introduction was not associated with later consumption of sweets, desserts and sweet-tasting beverages when adjustment for children's age was made among GDM+ and GDM children.

Conclusion: Early introduction of fruit juice in infant diet is associated with higher prevalence of consumption of>1 serving of fruit juice per day in GDM+ children.

Title page

Association between early introduction of fruit juice during infancy and childhood consumption of sweet-tasting foods and beverages among children exposed and unexposed to gestational diabetes mellitus *in utero*

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Introduction

Children born to mothers with gestational diabetes mellitus (GDM) are at high risk of developing obesity and type 2 diabetes later in life (Burguet, 2010; Nehring, Chmitorz, Reulen, von Kries, & Ensenauer, 2013). There is a lack of effective postnatal strategies to prevent these complications among these high-risk children (Dugas et al., 2017) although it is well established that healthy lifestyle behaviours are associated with a reduced risk of obesity among children in the general population (World Health Organization, 2012). On the other hand, despite efforts made to promote a healthy diet among children, consumption of high amounts of ultra-processed foods and beverages rich in free sugar, like fruit juice, sugar-sweetened beverages (SSB), pastries and candies is highly prevalent among Canadian children (Moubarac, Batal, Louzada, Martinez Steele, & Monteiro, 2017).

Preference for sweetness is innate among newborns and this preference generally remains during childhood (Ventura & Mennella, 2011). However, pre- and postnatal experiences, like exposure to different flavors during in utero and early postnatal periods, can modulate taste preferences (Birch & Marlin, 1982). The introduction of complementary foods in the infant diet represents also a critical period for flavor experiences in early life, particularly among non-breastfed children that have been exposed since birth to only the flavour of formula (Mennella, Reiter, & Daniels, 2016). Moreover, increasing evidence suggests that food preferences in children would depend on foods offered and the context of feeding during early life (Mennella et al., 2016). In fact, both healthy and unhealthy dietary patterns established during infancy can track into childhood (Rose, Birch, & Savage, 2017). Accordingly, some authors evaluated the association between SSB and fruit juice consumption in infancy and their later consumption in childhood and found that consumption of these types of beverages in early life was positively associated with their consumption during childhood (Park, Pan, Sherry, & Li, 2014; Sonneville et al., 2015). However, to our knowledge, no such study has been conducted among children exposed to GDM in utero. Given their in utero exposure to an environment rich in glucose, it is possible that taste development in these children could differ from children unexposed to GDM, particularly developmental preferences for sweet tasting foods, which could impact food habits. In fact, previous research has shown that fetal environment could be involved in food preferences programming (Portella et al., 2012).

While it is well recognized that SSB have a negative impact on children's health (Mirmiran, Yuzbashian, Asghari, Hosseinpour-Niazi, & Azizi, 2015), fruit juice is generally considered a healthier food option by parents. In fact, 100% fruit juice is considered as a serving of fruits in the 2007 Canada's Food Guide, which could encourage parents to introduce fruit juice early in their infant's diet (McElligott et al., 2012), without consideration for the sweet taste of this type of beverage. Thus, given that food habits could track from infancy to childhood (Nicklaus, Boggio, Chabanet, & Issanchou, 2005; Skinner, Carruth, Wendy, & Ziegler, 2002), and in order to identify new targets for prevention of obesity development among children exposed (GDM+) to GDM in utero, the primary objective of this study was to evaluate the association between early introduction of fruit juice during infancy and childhood consumption of sweet-tasting foods and beverages among GDM+ children. Secondly, we evaluated the association between early introduction of fruit juice and childhood consumption of sweet-tasting foods and beverages among a group of children unexposed (GDM-) to GDM in utero, in order to compare results between groups.

Material and methods

2.1. Population

All subjects were participants in a cohort study that aims to evaluate the impact of GDM on mother's and children's health and to examine whether a healthy postnatal environment could attenuate the adverse consequences of in utero exposure to GDM. This study takes place at the Institute of Nutrition and Functional Foods (INAF), at Laval University (Quebec City, Canada), and recruits women with and without a history of GDM and their children. Participants were recruited from a previous project conducted by our research team that has been previously described (Gingras, Paradis, Tchernof, Weisnagel, & Robitaille, 2012). Additionally, recruitment is conducted through access to medical records from the two major hospitals with a neonatal care unit in the metropolitan area of Quebec City (*Hôpital Saint-François d'Assise* and *Centre Hospitalier de l'Université Laval-CHUL*). Recruitment is also conducted by emails sent to Laval University community as well as posts on healthcare websites and on social media (Facebook). Children with a history of in utero exposure to GDM between 2003 and 2013 are included in the study and children exposed to type 1 or type 2 diabetes are excluded. Children from the control group had to be born to a mother that never have had diabetes (Type1, 2 or GDM) before or after the index pregnancy. To date, a total of 107 children exposed (GDM+) and 59 children unexposed (GDM-) to GDM in utero have participated in the project. Written consents were obtained from all participating mothers and children and ethical approval was obtained from the Laval University Ethics Committee (2011-196-A-4 R-3) and from the *Centre Hospitalier Universitaire de Québec* Ethics Committee (2015–2031). This study is registered in the Clinical Trials.gov registry (NCT01340924).

2.2. Exposure

Children came with their mother to the INAF research center for a single 1-hour visit. During this visit, data about the timing of fruit juice introduction were retrospectively collected by a self-administrated questionnaire completed by the mother of each child. Mothers were asked when their child drank fruit juice, defined as 100% pure juice, for the first time (infant age given in months and/or weeks). A randomly selected subsample of participants (n=20) completed this questionnaire for a second time at home, within a 2 weeks interval between each completion, in order to evaluate the reliability of answers given for this questionnaire. Results of the reliability test showed a strong correlation between answers given for the completion of both infant feeding questionnaires ($r=0.81$, $p < 0.001$).

2.3. Outcomes

In order to estimate current dietary intakes of children, a 24-hour dietary recall (24HDR) was conducted with a trained dietitian using the 5 steps of the Automated Multiple-Pass Method (AMPM): 1) quick list of the food items consumed 2) reminder of the food items frequently forgotten 3) time and type of meals 4) details about serving size consumed, brand name of commercial products, ingredients and methods of homemade foods 5) review of the dietary recall (Raper, Perloff, Ingwersen, Steinfeldt, & Anand, 2004). All food and drink items consumed in the previous day, from midnight to midnight, were recorded. Three-dimensional food models were used to enhance accuracy of portion size estimates. Mothers of children younger than 10 years were asked to complete the 24HDR whereas children were present during the interview and were asked to add information if needed (i.e. for food consumed outside home). For children ≥10 years, the 24HDR was completed directly by the child, with the help of the mother if needed (i.e. for food preparation details). A second 24HDR was completed over the phone with the mother following the same validated method, the AMPM (Raper et al., 2004), 7–10 days after their visit. Mean intakes for the two questionnaires were used in analyses. Dietary intake data were analyzed using Nutrition Data System for Research (NDSR) (Schakel, 2001; Schakel, Sievert, & Buzzard, 1988). From this software, reports can be extracted by nutrients or by food group categories for each participant. In order to extract data regarding sweet-tasting foods and beverages, the Nutrition Coordinating Center (NCC) Food Group Count System from NDSR was used (Schakel, 2001; Schakel et al., 1988). The NCC Food Group Count System is composed of 9 groups and 168 subgroups of foods, based on recommendations made by the Dietary Guidelines for Americans and the USDA Food Guide Pyramid. For the purpose of this study, groups and subgroups of foods containing high amount of sugar (Bernstein, Schermel, Mills, & L'Abbe, 2016) or known for their sweet taste were extracted and compiled together to form 4 foods and beverages groups. These groups were used in analyses, with a description of a portion size provided bellow:

1) Fruit juice, defined as 100% pure juice, which include citrus and non-citrus juice (125 ml).

2) Sweet-tasting beverages (STB), which include sweetened and artificially sweetened soft drinks, fruit drinks, tea and water (125 ml).

3) Desserts, which include cakes (55 g–125 g), cookies (30 g), pies, cobblers and pastries (125 g), danish and doughnuts (55 g).

4) Sweets, which include sugar (4 g), syrup (30–60 ml), honey, jam and molasses (15 ml), fudge, caramel and chocolate syrup (30 ml), candy, chocolate candy and gum drops (40 g), frosting or glaze (35 g) and sweetened flavored milk beverage powder (1 cup prepared).

Children were categorised as non-consumers (0 serving/d), consumers (> 0 serving/day) or high consumers (> 1 serving/day) of the 4 different sweet-tasting food and beverage groups described above.

2.4. Statistical analyses

Descriptive statistics were calculated as mean ± standard deviation (SD) or as percentage (%). Participant's characteristics and dietary intakes during childhood of GDM+ and GDM-children were compared using Student t-test, Chi-squared test (χ^2) or Fisher's exact test (when cell number was <5). GDM+ and GDM-children were divided into groups according to the median timing of fruit juice introduction during infancy, which was 9 months. Fisher's exact test and χ^2 test were performed to evaluate the distribution of children across different groups of consumers and high consumers of sweet tasting food and beverages among GDM+ and GDM-children. Finally, prevalence ratios (PR) using log binominal model were calculated to evaluate the prevalence of consumers and high consumers of food items from the different food groups in children introduced to fruit juice before 9 months compared to those introduced at 9 months or later among GDM+ and GDM- children. Given the low prevalence of children who consumed >1 serving of STB per day in both groups, the PR of high consumption of STB was not computed. Finally, stepwise regression analyses were performed to determine which cofactors should be included in the adjusted models among the following: breastfeeding duration, timing of solid food introduction, children's sex and age, maternal education level and family incomes. Accordingly, analyses were only adjusted for children's age. The p value$\leq$0.05 and confidence interval (CI) of 95% were used to identify statistically significant results. SAS software, version 9.4, was used for analyses.

Results

A total of 107 GDM+ and 59 GDM- children were recruited, but only 62 GDM+ and 32 GDM- children had complete information regarding the timing of fruit juice introduction. Within the subsample with missing information, 9 mothers did not answer the specific question regarding the timing of fruit juice introduction and 63 gave the answer “I don't’ know” to this question. Thus, analyses included the 94 children with complete information. Among GDM+ children without data on fruit juice introduction (n = 45), a lower proportion had been breastfed compared to children included in analyses (80% compared to 95%, p = 0.03). However, there was no difference regarding children's age and sex, maternal education level, family incomes and the timing of solid food introduction (results not shown). There was also no statistically significant difference in characteristics of GDM- children included and excluded from analyses. Characteristics of the 94 participating children are presented in **Table 1**. Overall, 77% and 78% of GDM+ and GDM- children received fruit juice during the first year of life, respectively.

During childhood, the average consumption of fruit juice was 0.92 serving of 125 ml per day for GDM+ and 1.13 servings for GDM- children, including children that did not consume any amount of fruit juice (**Table 2**). Among the consumers only, mean intake was 1.96 and 1.65 servings of 125 ml per day for GDM+ and GDM- children, respectively (results not shown). Similarly, mean intake for STB was 0.69 and 0.79 serving per day for all GDM+ and GDM- children, respectively (**Table 2**). However, the average consumption of STB among consumers only was 1.02 and 0.94 serving of 125 ml per day for GDM+ and GDM- children, respectively (results not shown). Frequency of consumption of any amount of fruit juice per day tended to be higher among GDM- than GDM+ children (p = 0.05, **Table 2**).

Among GDM+ children, consuming>125 ml of fruit juice per day was more frequent among children introduced to fruit juice earlier, i.e. before 9 months, compared to those introduced at 9 months or later (**Table 3**). Still among GDM+ children, the same pattern was seen for STB that were more frequently consumed, for any amount of STB as well as for>125 ml/d, among GDM+ children exposed to fruit juice earlier. However, no statistically significant difference was seen for the distribution of children who reported consuming any amount of desserts, sweets or fruit juice (> 0 serving/d) or for high consumers of sweets and desserts (> 1 serving/d), between GDM+ children exposed to fruit juice before and ≥9 months (**Table 3**). Among GDM- children, any amount of desserts tended to be more frequently consumed among children introduced to fruit juice<9 months (73.7% of consumers) compared to those introduced to fruit juice ≥9 months (26.3% of consumers, p=0.05, **Table 3**). No other difference was seen in the distribution of consumption of any food and beverage groups among GDM- children (**Table 3**).

As seen in **Table 4**, GDM+ children introduced to fruit juice before 9 months did not have different PR for the consumption of any amount of fruit juice, sweets and desserts compared to GDM+ children introduced to fruit juice ≥9 months. However, consuming more than 125 ml of fruit juice per day was 2.72 times more prevalent among GDM+ children introduced to fruit juice before 9 months, compared to those introduced at 9 months or later (CI: 1.19–6.20). Although prevalence of consumption of any amount of STB in the crude model was 2.11 higher for GDM+ children exposed to fruit juice earlier (CI: 1.02–4.34, result not shown), this latter was no longer statistically significant after adjustment for children's age (PR: 1.43, CI: 0.85–2.42, **Table 4**). Among GDM- children, the prevalence for the consumption of any amount or for>1 serving of any food and beverage groups was similar according to the timing of fruit juice introduction (**Table 4**). Given the small number in some cells, adjusted prevalence ratio could not be computed in some models.

Discussion

This study showed that early introduction of fruit juice during infancy, defined as before 9 months of age, is associated with a higher odds of consuming sweetened and artificially sweetened beverages and high amounts of fruit juice during childhood among GDM+ children. The association between the timing of fruit juice introduction and odds of consuming>125 ml of fruit juice per day remained statistically significant after adjustment for children's age, but the association between fruit juice introduction and later consumption of STB was no longer statistically significant after adjustment for children's age. Among GDM- children, no statistically significant association between the timing of fruit juice introduction and consumption of sweet-tasting food and beverages during childhood was observed.

Results of this study suggest that the prevalence of consumption of more than 1 serving of fruit juice per day was higher among GDM+ children exposed to fruit juice before 9 months compared to those exposed to juice at or after 9 months. To our knowledge, this is the first study that evaluated the association between early life nutrition and food and beverage intakes during childhood among GDM+ children, which limits comparison of these results with the current literature. However, few studies conducted in the general population that investigated the association between SSB or juice intakes in infancy and beverage consumption in childhood showed similar results that these found in the GDM+ group (Park et al., 2014; Sonneville et al., 2015). Analyses from the Infant Feeding Practices Study II (IFPS II), a national longitudinal study conducted in the United-States, showed that consuming SSB during the first year of life was associated with an increased risk of consuming SSB more than one time per day at the age of 6 years (Park et al., 2014). In addition, Sonneville et al. showed that higher intakes of fruit juice at the age of 12 months was associated with a higher consumption of fruit juice and SSB in both early and midchildhood when compared to infant that did not consume any amount of fruit juice at 12 months (Sonneville et al., 2015). More specifically, children consuming ≥16 oz of juice per day at 1 year consumed twice as much juice per day during childhood compared to those that did not consume any amount of juice at 1 year (2.4 vs 1.2 servings per day) (Sonneville et al., 2015).

Our study showed no statistically significant association between the timing of fruit juice introduction during infancy and later consumption of foods containing high amount of sugar among GDM+ children. To our knowledge, no study has evaluated the association between juice introduction in infancy and later consumption of sweet foods in children exposed or unexposed to GDM in utero. However, Rose et al. evaluated the association between dietary patterns in early life and dietary patterns in childhood using data from the IFPS II (Rose et al., 2017). This study showed that infants having a high density energy diet at 9 months, which included high amounts of juice, sweet foods and French fries, were greater consumers of SSB, sweet desserts and fried potatoes at 6 years, compared to other dietary patterns in infancy (Rose et al., 2017). Liquid and solid foods have different properties. Indeed, sugars from liquid sources are associated with less satiety compared to sugar from solid foods, mainly due to the different fiber content (Pan & Hu, 2011). However, we are unaware of any published study evaluating the influence of the food matrix on taste development, thus it is unclear whether sugar intake from juice could affect taste preference for sugar from solid foods the same way that for sugar from liquids.

Furthermore, this study showed no statistically significant association between the timing of fruit juice introduction and later consumption of sweet tasting food and beverages among GDM- children. The lack of association in the control group, which is not in agreement with studies conducted in the general population (Park et al., 2014; Rose et al., 2017; Sonneville et al., 2015), could possibly be explained by the small number of participants in the GDM- group, which limits the statistical power to detect statistically significant results.

The association between the timing of fruit juice introduction in infant diet and beverages consumption in childhood among GDM+ children could be explained in part by the development of taste preferences in early life. As mentioned earlier, it has been demonstrated that taste preferences track from infancy to childhood and that the early life period could be a critical moment to program children's dietary habits (Mennella et al., 2016). In fact, nutritional experiences in early life have neurological programing effect that influence eating behaviour later in life (Trabulsi & Mennella, 2012). A study conducted in mice that evaluate the neuroanatomical development of the olfactory system showed that exposure through mother's milk to odours that activate GFP-tagged olfactory receptors was associated with larger glomeruli in the olfactory bulb and with significant preferences for the activating odour (Todrank, Heth, & Restrepo, 2011). These results suggest that exposure to specific flavours during early life result in enhanced detection of these learned odours, which could facilitate their acceptance by children. Among studies conducted in humans, Pepino et al. demonstrated that infants who were routinely fed with sweet water in early life preferred high levels of sucrose in childhood, compared to those who were not routinely fed with sweet water in infancy, highlighting the impact of early exposure to sweet on modulation of taste preference for sweetness (Pepino & Mennella, 2005). However, even if the early life period is recognized as critical for the development of taste preferences, the exact timing to shift taste preferences is still unknown (Mennella & Bobowski, 2015). In order to answer this gap, a randomized clinical trial has been conducted among formula-fed infants to test whether the timing of introduction of protein hydrolysate formulas (PHF), known for their particularly unpleasant flavour, in infant diet would influence its acceptance later in infancy (Mennella, Lukasewycz, Castor, & Beauchamp, 2011). This study showed that infant exposed to PHF earlier (i.e. at 1.5 and 2.5 months) consumed significantly more amount of PHF at 7.5 months compared to infants exposed later (i.e at 3.5 months) (Mennella et al., 2011). Infants exposed to PHF at 3.5 months consumed the same amount of PHF at 7.5 months as infants from the control group who were fed with cow-milk base formulas (Mennella et al., 2011). Thus, authors suggested that the window of opportunity to modulate taste preferences could start to close as early as 3.5 months.

Although we first hypothesized that early introduction of fruit juice in the infant diet would lead to an increased consumption of sweet tasting foods and beverages, we only found associations with beverage intakes. As mentioned above, it is possible that the food matrix of juice, a liquid with no fiber, would influence differently the consumption of beverages and solid foods because of their different properties (Pan & Hu, 2011). Furthermore, in addition to the taste preference theory, it has been suggested that fruit juice intake in infancy could be a gateway to later consumption of caloric beverages by establishing the habit of consuming these types of drinks (Sonneville et al., 2015). Similarly, the association between the timing of fruit juice introduction and its later consumption could also be explained by dietary habits established by parents during infancy that could remain during childhood. In fact, it is possible to think that parents continue to feed their children the same types of food from infancy to childhood, explaining associations seen for beverages but not for foods.

Our study presents some limitations. First, given the cross-sectional study design, the timing of fruit juice introduction was retrospectively collected. This did not allow us to quantify the amount of juice intakes in infant diet neither the frequency of consumption during this period, which can have an impact on taste development and dietary habits. This study design is also at risk of recall bias, although our reliability test showed a strong correlation between answers given for the two completed questionnaires. Furthermore, mothers had the possibility to answer “I don't know” to the question regarding the timing of juice introduction, which reduces risk of recall bias in our analyses. In fact, it is possible to think that mothers that answered this question were confident of their answer. However, this study should be repeated using a prospective study design in order to limit this bias. Another limitation of the study is its small sample size, in both the GDM+ and GDM- groups, which increases the likelihood of type 2 error. Indeed, given the small sample size of participants in the control group (n = 32), it is possible that the lack of association observed in this group is due to low statistical power. Furthermore, the homogeneity of participant's characteristics (high income families with high education level) restricts our results to this study population only. Finally, this study did not evaluate specifically taste preferences of children, which limits interpretation of these results. In fact, Divert et al. showed that consumption of sweet tasting foods and beverages was not clearly associated with sweet liking, evaluated using a liking score, in a cohort study of school-aged children (Divert et al., 2017). Despite these limitations, this study presents several strengths. This is, to our knowledge, the first study that evaluated the impact of early life nutrition on dietary habits during childhood among children exposed to GDM in utero, a population at high-risk of many health problems such as obesity (Nehring et al., 2013). Another strength is the use of two 24HDR to evaluate current dietary intakes of children. This allowed us to have quantitative data regarding food group intakes, while other studies generally use semiquantitative questionnaires (Park et al., 2014; Sonneville et al., 2015). The use of two recalls, as it has been done by others in large population studies (Ahluwalia, Dwyer, Terry, Moshfegh, & Johnson, 2016; Devaney et al., 2004; Health Canada, 2006), helps to reduce the day-today variability of dietary intakes measured with 24HDR while minimizing the burden on participants (Naska, Lagiou, &

Lagiou, 2017, p. 926, p. 926). Finally, the fact that dietary questionnaires were conducted by a trained dietitian minimized risk of food misclassification, especially for fruit juice and fruit drinks.

Conclusion

This study suggests that early introduction of fruit juice in the infant diet is associated with higher prevalence of consumption of high amounts of fruit juice in GDM+ children. Further studies using a prospective study design in a larger cohort will be necessary to investigated whether delaying or avoiding the introduction of fruit juice in infancy could be a promising strategy to improve dietary habits, with possible lower consumption of high caloric foods, and therefore, prevent obesity among this high-risk population of children.

Conflicts of interest

None.

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Tables

Table 7. 1 Participants' characteristics

Characteristics		Mean ± SD or n (%)		
		GDM+ N=62	GDM- N=32	P value
Demographic				
Age (years)		6.3±2.6	7.6±3.7	0.08
	2-5 (years)	29 (47.8)	12 (37.5)	0.10
	6-9 (years)	25 (40.3)	10 (31.3)	
	10-14 (years)	8 (12.9)	10 (31.3)	
Sex				
	Boys	32 (51.6)	11 (34.4)	0.12
	Girls	30 (48.4)	21 (65.6)	
BMI z-score (kg/m2)		0.04±0.98	-0.01±0.70	0.76
Family income (CAD$/year)				
	0 – 39 000	4 (7.7)	3 (11.5)	0.48
	40 000 – 79 000	20 (38.5)	9 (34.6)	
	80 000- 99 999	13 (25.0)	3 (11.5)	
	>100 000	15 (28.9)	11 (42.3)	
Maternal education level				
	High school	12 (21.8)	4 (15.4)	0.65
	College	7 (12.7)	2 (7.7)	
	University	36 (65.5)	20 (76.9)	
Maternal age		38.0±4.2	37.1±4.5	0.33
Maternal BMI		27.7±7.7	26.2±5.0	0.24
Parity		2±0.7	2±0.6	0.62
Infant feeding practices				
Breastfed infants[a]		58 (95)	27 (93)	0.66
Breastfeeding duration (months)[b]		8.9±7.8	10.1±4.6	0.39
Age of solid food introduction (months)[c]		4.9±1.0	4.9±1.3	0.81
Age of fruit juice introduction (months)		8.7±3.0	7.6±3.7	0.13

Results are presented as mean ± SD or n (%) and were compared using Student t-test, chi-square test or Fisher's exact test. BMI: body mass index. [a]n=61 for GDM+ and n=29 for GDM-. [b]n=57 for GDM+ and n=27 for GDM-. [c]n=59 for GDM+ and n=29 for GDM-.

Table 7. 2 Dietary intakes during childhood

		Mean ± SD or n (%)	
Food groups		**GDM+**	**GDM-**
Fruit juice			
	Consumers (yes)	29 (46.8)	22 (68.8)*
	High consumers (>125 ml/d)	18 (29.0)	11 (34.4)
	Mean intake (servings of 125 ml/d)	0.92±1.57	1.13±1.36
STB			
	Consumers (yes)	21 (33.9)	14 (43.8)
	High consumers (>125 ml/d)	9 (14.5)	3 (9.4)
	Mean intake (servings of 125 ml/d)	0.69±1.41	0.79±1.38
Sweets			
	Consumers (yes)	50 (80.6)	25 (78.1)
	High consumers (>1 serving/d)	10 (16.1)	6 (18.8)
	Mean intake (serving/d)	0.44±0.50	0.63±1.16
Desserts			
	Consumers (yes)	38 (61.3)	19 (59.4)
	High consumers (>1 serving/d)	15 (24.2)	7 (21.9)
	Mean intake (serving/d)	0.69±1.02	0.49±0.57
Energy intake (kcal)		1686±439	1790±585

Fruit juice includes citrus and non-citrus 100% pure juice; **sweet-tasting beverages** (STB) include sweetened and artificially sweetened soft drinks, fruit drinks, tea and water; **sweets** include sugar, syrup, honey, jam, molasses, fudge, caramel, chocolate syrup, candy, chocolate candy, gum drops, frosting or glaze and sweetened flavored milk beverage powder; **desserts** include cakes, cookies, pies, pastries, danish, doughnuts and cobblers. *p=0.05.

Table 7. 3 Association between the timing of fruit juice introduction and consumption of sweet-tasting foods and beverages during childhood among GDM+ and GDM- children

		Introduced to juice < 9 months	Introduced to juice ≥ 9 months	
Childhood consumption		N (%)	N (%)	p
GDM+ children				
Fruit juice	Yes	15 (51.7)	14 (48.3)	0.22
	>125 ml	12 (66.7)	6 (33.3)	**0.02**
STB	Yes	13 (61.9)	8 (38.1)	**0.04**
	>125 ml	8 (88.9)	1 (11.1)	**0.008**
Desserts	Yes	20 (52.6)	18 (47.4)	0.07
	>1 serving	8 (53.3)	7 (46.7)	0.38
Sweets	Yes	24 (48.0)	26 (52.0)	0.10
	>1 serving	6 (60.0)	4 (40.0)	0.25
GDM- children				
Fruit juice	Yes	12 (54.5)	10 (45.5)	0.22
	>125 ml	8 (72.7)	3 (27.3)	0.17
STB	Yes	10 (71.4)	4 (28.6)	0.14
	>125 ml	2 (66.7)	1 (33.3)	0.45
Desserts	Yes	14 (73.7)	5 (26.3)	0.05
	>1 serving	5 (71.4)	2 (28.6)	0.27
Sweets	Yes	15 (60.0)	10 (40.0)	0.33
	>1 serving	3 (50.0)	3 (50.0)	0.31

The group "yes" refers to children who reported having consumed any amount of items from the specific food group. **Fruit juice** includes citrus and non-citrus 100% pure juice; **sweet-tasting beverages** (STB) include sweetened and artificially sweetened soft drinks, fruit drinks, tea and water; **sweets** include sugar, syrup, honey, jam, molasses, fudge, caramel, chocolate syrup, candy, chocolate candy, gum drops, frosting or glaze and sweetened flavored milk beverage powder; **desserts** include cakes, cookies, pies, pastries, danish, doughnuts and cobblers. P value was calculated with χ^2 analyses and with Fisher's exact test when cell number was <5.

Table 7. 4 Prevalence of consumption of sweet-tasting foods and beverages in GDM+ and GDM-children introduced to fruit juice<9 months compared to those introduced at or after 9 months of age.

		Prevalence ratio	95% CI
GDM+ children			
Fruit juice	Yes	1.56	(0.93; 2.60)
	>125 ml	**2.72**	**(1.19; 6.20)**
STB	Yes	1.43	(0.85; 2.42)
Desserts	Yes	1.44	(0.97; 2.13)
	>1 serving	1.42	(0.58; 3.49)
Sweets	Yes	1.19	(0.94; 1.51)
	>1 serving	-	-
GDM- children			
Fruit juice	Yes	-	-
	>125 ml	1.67	(0.51; 5.45)
STB	Yes	1.47	(0.55; 3.97)
Desserts	Yes	1.63	(0.72; 3.71)
	>1 serving	-	-
Sweets	Yes	0.96	(0.64; 1.43)
	>1 serving	0.35	(0.07; 1.61)

Log-binominal regression analyses showing prevalence ratios with 95% CI for consumption of fruit juice, sweet-tasting beverages (STB), sweets, desserts, >125 ml of fruit juice and >1 serving of sweets and dessert in GDM+ and GDM- children introduced to fruit juice before 9 months compared to those introduced at 9 months or later (reference group). Increase prevalence of children consuming these food groups are above the 95% confidence limit of an agreement ratio of 1.00. Results presented are adjusted for children's age.

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Chapitre 8 Est-ce qu'une saine alimentation est associée à de plus faibles altérations anthropométriques et glycémiques chez des enfants à risque ayant été exposés au diabète gestationnel?

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L'article présenté dans ce chapitre s'intitule: *Is A Healthy Diet Associated with Lower Anthropometric and Glycemic Alterations in Predisposed Children Born from Mothers with Gestational Diabetes Mellitus?*

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Résumé

Les enfants nés de femmes ayant eu un diabète gestationnel (DG) sont à risque élevé de développer de l'obésité et le diabète de type 2. À ce jour, peu de stratégies de prévention efficaces de ces complications ont été identifiées. L'objectif de cette étude était d'évaluer l'association entre la qualité de l'alimentation et les profils anthropométrique et métabolique des enfants exposés (DG+) ou non-exposés (DG-) au DG. Un total de 104 enfants DG+ et 38 DG– ont été inclus. Deux rappels alimentaires de 24h ont été utilisés pour évaluer les apports alimentaires des enfants. Le score de la qualité de l'alimentation *Healthy Eating Index* adapté pour la population canadienne (HEI-C) a été utilisé pour évaluer la qualité de l'alimentation des enfants. Des corrélations de Spearman ajustées pour l'âge et le sexe de l'enfant ont été réalisées. L'âge moyen était de 6,0 ± 2,5 et 6,8 ± 2,3 ans pour les enfants DG+ et DG-, respectivement (p = 0,03). Le score HEI-C total était négativement associé au ratio de masse grasse androïde sur gynoïde (r = -0,29, p = 0,03) et avec l'index de résistance à l'insuline (HOMA-IR) (r = -0,22, p = 0,04) chez les enfants DG+ seulement. La prévalence de surplus de poids ou d'obésité pendant l'enfance était quatre fois supérieure chez les enfants DG+ ayant un score HEI-C ≤70 comparativement aux enfants DG+ ayant un score HEI-C >70. Les résultats de cette étude suggèrent qu'une saine alimentation serait associée à un meilleur profil cardiométabolique chez les enfants DG+, incluant un risque réduit de surplus de poids ou d'obésité.

Abstract

Children born from mothers with gestational diabetes mellitus (GDM) are at high-risk of obesity and type 2 diabetes. To date, there is a lack of effective strategies to prevent these complications. The aim of this study was to evaluate the association between diet quality and anthropometric and glycemic profiles of children exposed (GDM+) and unexposed (GDM–) to GDM. A total of 104 GDM+ and 38 GDM– children were included. Two 24-h dietary recall questionnaires were used to assess dietary intakes. The Healthy Eating Index adapted for the Canadian population (HEI-C) was used to assess diet quality. Spearman correlations adjusted for children's age and sex were computed. Mean age was 6.0 ± 2.5 and 6.8 ± 2.3 years for GDM+ and GDM–, respectively ($p = 0.03$). Total HEI-C score was negatively associated with the android-to-gynoid fat mass ratio ($r = -0.29$, $p = 0.03$) and homeostasis model assessment for insulin resistance (HOMA-IR) index ($r = -0.22$, $p = 0.04$) in GDM+ children only. The prevalence of being overweight or obese during childhood was 4-fold higher among GDM+ children with a HEI-C score ≤70 compared to GDM+ children with a HEI-C score >70. Results of this study show that a healthy diet is associated with a better cardiometabolic health profile in GDM+ children, including a lower risk of being overweight or obese.

Title page

Is A Healthy Diet Associated with Lower Anthropometric and Glycemic Alterations in Predisposed Children Born from Mothers with Gestational Diabetes Mellitus?

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Introduction

Gestational diabetes mellitus (GDM), defined as hyperglycemia with first onset or recognition during pregnancy[1], is associated with health consequences for the child exposed in utero[2,3]. Indeed, in utero exposure to high glucose levels enhances fetal growth and fat deposition and contributes to the high risk of developing obesity later in life [4]. Accordingly, we have previously shown that children born from mothers with GDM (GDM+) have alterations in body fat proportion and distribution at 6 years of age when compared to children unexposed to GDM (GDM–) during pregnancy[5]. In utero exposure to GDM is also associated with a higher risk developing type 2 diabetes later in life through increased fetal insulin secretion and altered pancreatic function [6,7].

Although efforts have been made to prevent GDM development among pregnant women[8,9], there is currently a lack of effective postnatal strategies to prevent obesity and type 2 diabetes among these high-risk children[10]. Although it is well established that a healthy diet is associated with better cardiometabolic health in children [11,12], little is known regarding the impact of diet quality on anthropometric and glycemic profiles among GDM+ children, a group at high risk.

Assessment of diet quality can be made using various methods. In 2009, a Canadian version of the American Healthy Eating Index (HEI-C) was developed and validated in the Canadian population aged of 2 years or more [13]. This score provides an overall rating of the adherence to the 2007 Canadian Food Guide (CFG) recommendations and therefore, facilitates the evaluation of diet quality. Accordingly, the aim of this study was to assess the association between diet quality, using the HEI-C score, and anthropometric and glycemic profiles of GDM+ and GDM– children. We found that adopting a healthy diet was associated with more favorable anthropometric and glycemic profiles in GDM+ children. Interestingly, overweight or obesity was four-fold less prevalent in children with a high HEI-C score.

Materials and methods

2.1. Study Population

All children were participants of a cohort study that aims to evaluate the impact of GDM on maternal and offspring health and to examine whether a healthy postnatal environment could attenuate the adverse consequences of in utero exposure to GDM. This project has been previously described[14]. Briefly, this study is conducted at the Institute of Nutrition and Functional Foods (INAF), at Laval University (Quebec City, Canada), and recruits women with or without a history of GDM and their children born between 2003 and 2013 and aged between 2 and 14 years in the metropolitan area of Quebec City. Recruitment has been conducted using medical records from the two major hospitals with a neonatal care unit in the area of Quebec City (*Hôpital Saint-François d'Assise* and *Centre Hospitalier de l'Université Laval*) and administrative data from the provincial health plan registry (*Régie de l'assurance maladie du Québec*), as well as email addresses of student and employees of the Laval University Community. Children exposed to GDM in utero were recruited and children exposed to either type 1 or type 2 diabetes during pregnancy were excluded from the project. The majority of children included (92%) were born before 2013, i.e., when GDM was diagnosed with 2003 criteria of Diabetes Canada[15]. Children from the control group had to be born from a mother without a history of GDM, type 1 or type 2 diabetes. Written consent was obtained from all participating mothers and children and ethical approval was obtained from the Laval University Ethics Committee (2011-196-A-4 R-3) and from the *Centre Hospitalier Universitaire de Québec* Ethics Committee (2015–2031). This cohort study was registered in the Clinical Trials.gov registry (NCT01340924).

2.2. Food Assessment

Children came to the INAF research center for a single 1-hour visit with their mother where current dietary intakes were assessed as described previously[16]. Briefly, a 24-h dietary recall questionnaire (24HDR) was conducted with a trained dietician using the multiple-pass method[17]. All items consumed from midnight to midnight the previous day were listed. To enhance accuracy of portion size estimates, three-dimensional food models were used. For children younger than 10 years, the 24HDR was completed with mothers while children were present during the interview and were asked to add information if needed (i.e., for food consumed outside the home). For older children (≥10 years), the 24HDR was conducted directly with the child, with the help of the mother if needed (i.e., for food preparation details). A second 24HDR was conducted over the phone, 7–10 days after the visit at the research center, using the same validated method[17].

The HEI-C score is based on the American Index but is adapted to the Canadian population by using number of servings, according to age and sex, defined in the 2007 version of CFG[13]. The HEI-C score has been validated in the Canadian population aged 2 and over using data from the 2004 Canadian Community Health Survey–Nutrition[13]. Briefly, the HEI-C score is composed of eleven components, which includes eight adequacy components (total vegetables and fruit, whole fruit, dark green and orange vegetables, total grain products, whole grains, milk and alternatives, meat and alternatives, and unsaturated fats) and three moderation components (saturated fats, sodium, and "other food")[13]. Adequacy components represent food items that should be consumed in high amounts in order to achieve a healthy diet (high intakes are associated with high adequacy scores) whereas moderation components represent foods that should be limited in a healthy diet (low intakes are associated with a high moderation score). The maximal possible score is 100, with adequacy components contributing to 60 points and moderation components to 40 points[13]. Good diet quality is defined as a score >80; a score between 50 and 80 corresponds to diet that requires improvement while a score <50 is associated with poor diet quality[13]. Mean intakes from the two 24HDR were used to calculate the HEI-C total score and its components. Number of servings per day for each food group (vegetables and fruit, grain products, milk and alternatives, meat and alternatives) according to 2007 CFG serving size were calculated[18]. The whole fruit component was obtained by excluding fruit juice from the total fruit group[19]. However, fruit juice was part of the total vegetables and fruit group. The 2007 Canadian classification was used to calculate the whole grains component as well as the dark-green and orange vegetables component, which includes some orange fruits rich in vitamin A such as apricots, peaches, cantaloupes, mango, nectarines, and papayas[20]. The "other food" component was derived from a list of foods and beverages that are mostly fats and sugars, as described in the CFG[18]. Unsaturated fats, saturated fats, and sodium components were extracted using Nutrition Data System for Research software (NDSR version 2011, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA).

2.3. Outcomes

Height was measured to the nearest 0.1 centimeter using a stadiometer, weight was measured to the nearest 0.1 kilogram using a calibrated balance (Tanita BC-418) and body mass index (BMI) was calculated (kg/m2). BMI z score was calculated using World Health Organization (WHO) Anthroplus software (version 1.0.4, WHO, Geneva, Switzerland). A BMI z score >2 for children younger than 5 years and BMI z score >1 for children of 5 years or more were used to define overweight or obesity status according to the WHO classification[21,22]. Waist circumference was measured twice, at the umbilical level, to the nearest millimeter and the mean of the two measurements was used in analyses[23]. Body composition was measured by dual-energy X-ray absorptiometry scanner (DEXA, GE Healthcare Lunar; Madison, WI, USA). Fat mass percentage and fat mass distribution (gynoid and android fat mass percentage) of children were analyzed as previously described[5]. The android-to-gynoid fat mass ratio was calculated. Blood samples were collected after a 12-h fast. Plasma glucose was measured enzymatically [24] and plasma insulin was measured by electrochemiluminescence (Roche Diagnostics, Indianapolis, USA). To measure glycated hemoglobin (HbA1c) levels, the Cobas Integra 800 standardized to the National Glycated Hemoglobin Standardization Program (Integra Inc., Roche, Switzerland) was used. The homeostasis model assessment for insulin resistance (HOMA-IR) index was calculated as follows: ((Fasting insulin (pmol/L)/6.945) x fasting glucose (mmol/L))/22.5[25].

2.4. Other Measurements

Socioeconomic data were collected by a self-administered questionnaire completed by the mother. Maternal GDM status and the type of treatment used during pregnancy (i.e., medication (98.3% insulin and 1.7% oral hypoglycemic agents) or diet) were self-reported by the mother. Actual maternal body weight was measured to the nearest 0.1 kg using a calibrated balance (Tanita BC-418), height was measured on a standing position to the nearest millimeter and BMI was calculated.

2.5. Statistical Analyses

Descriptive characteristics were calculated as mean standard deviation or as percentage (%). Participant's characteristics and diet quality were compared between the GDM+ and GDM– groups using Student's t-test, chi-squared test (χ^2), and ANOVA. Spearman rank correlations were computed to assess the association between diet quality (HEI-C score and its components) and anthropometric or glycemic profiles of GDM+ and GDM– children. Adjustments for children's age and sex were performed. Prevalence ratio (PR) using log binominal models were calculated to evaluate the prevalence of overweight or obesity in GDM+ children with a diet quality under the median HEI-C score (i.e., $\leq$70), compared to GDM+ children with a HEI-C score above the median. The low prevalence of children with a good quality diet (i.e., score >80) did not allow us to compare the prevalence of overweight or obesity according to this cut-off. Furthermore, given the small number of GDM– children with overweight or obesity (n = 3), PR for this group was not computed. Finally, the proportion of overweight or obese children according to the median HEI-C score have been compared using a χ^2 test. A p-value <0.05 and confidence interval (CI) of 95% were used to determine statistical significance. The statistical software SAS studio was used (SAS Institute Inc., Cary, NC, United States).

Results

3.1. Participant's Characteristics

A total of 104 GDM+ and 38 GDM– children with available nutritional data were included in this study. As shown in **Table 1**, GDM+ children were younger than GDM– children (6.0 ± 2.5 and 6.8 ± 2.3 years, respectively, $p = 0.03$). Furthermore, GDM+ children presented altered anthropometric and glycemic profiles compared to GDM– children as published previously (**Table 1**)[5].

There was no difference between mean HEI-C score in GDM+ and GDM– children, although mean intakes of components of the score were different between groups (**Table 2**). In fact, GDM+ children ate less whole fruits and grain products and more meat and alternatives as well as saturated fats than GDM–children ($p < 0.05$, **Table 2**).

3.2. Diet Quality and Anthropometric and Glycemic Profiles of Children

Among GDM+ children, the total HEI-C score was negatively associated with android-to-gynoid fat mass ratio ($r = -0.29$, $p = 0.03$) and HOMA-IR index ($r = -0.22$, $p = 0.04$) (**Tables 3 and 4**) but was not significantly associated with anthropometric or glycemic profiles among GDM– children (**Tables 3 and 4**). Components of the HEI-C score were associated differently to anthropometric and glycemic profiles in GDM+ versus GDM– children (**Tables 3 and 4**). More specifically, higher intakes of total grain products as well as milk and alternatives were associated with a less central adipose tissue distribution among GDM+ children. Lower intake of foods rich in fats and sugars (higher"other foods" score) was associated with lower HbA1c levels in GDM+ children ($p < 0.05$, **Table 4**). Among GDM– children, higher intakes of total grains as well as whole grains were associated with lower gynoid fat mass percentage ($p < 0.05$, **Table 3**). In addition, among GDM– children, higher intakes of whole fruits, dark green or orange vegetables as well as unsaturated fats were associated with a better anthropometric profile ($p < 0.05$, **Table 3**).

Finally, the prevalence of being overweight or obese during childhood was 4-fold higher among GDM+ children with a low HEI-C score, i.e., ≤70, compared to GDM+ children with a HEI-C score above 70 (PR: 4.01, confidence interval (1.21–13.26). Furthermore, a higher proportion of overweight or obese children had a diet quality below the median HEI-C score of 70 (**Table 5**).

Discussion

Results of this study suggest that a healthy diet is associated with better anthropometric and glycemic profiles among GDM+ children. Indeed, the total HEI-C score was negatively associated with the android-to-gynoid fat mass ratio and HOMA-IR index in GDM+ children. Furthermore, the prevalence of being overweight or obese during childhood was 4-fold higher among GDM+ children with a HEI-C score ≤70 compared to GDM+ children with a HEI-C score >70. Finally, higher scores of total grain products as well as milk and alternatives scores were associated with a better anthropometric profile, including a more favorable adipose tissue distribution, i.e., less central adipose tissue distribution, and lower intakes of sugars and fats were associated with lower HbA1c values among GDM+ children.

We showed that a healthy diet, as assessed with the total HEI-C score, was associated with a more favorable adipose tissue distribution, i.e., with a lower android-to-gynoid fat mass ratio, and a lower insulin resistance state among GDM+ children. In addition, among GDM+ children, a HEI-C score ≤70 was associated with an increased prevalence of overweight or obesity when compared to a HEI-C score >70. To our knowledge, this is the first study assessing the association between diet quality and cardiometabolic health of GDM+ children, which limits comparisons with the current literature. However, this is consistent with a study from the general population. Indeed, among 630 Canadian children at risk of overweight from the Quebec Adiposity and Lifestyle Investigation in Youth (QUALITY) cohort, poor diet quality, defined as a “fast food” eating pattern, was associated with overweight and higher adiposity measurements during childhood[26]. In a similar manner, it has been shown that an energy-dense, high-fat, low-fiber diet was associated with greater adiposity levels or higher odds of excess adiposity in childhood [27,28]. Moreover, in a sample of children from Iran, the total HEI score was negatively associated with insulin resistance state [29].

This study also suggests that grain products were associated with a better anthropometric profile in both groups. These results are consistent with results from the National Health and Nutrition Examination Survey III study showing that adolescents in the lowest quartile of waist circumference consumed one more serving of grain products per day, compared to those in the highest quartile of waist circumference [30]. In that previous study, waist circumference was negatively associated with both whole- and refined-grain consumption [30]. Furthermore, prospective data from the Women, Infants and Children (WIC) program showed that each increase of one serving of breads and grains per day was associated with a decrease of 0.16 kg in infant and children bodyweight [31].

We also found that milk and alternatives component was negatively associated with android-to-gynoid fat mass ratio among GDM+ children, suggesting a better fat mass distribution with higher intakes of milk and alternatives. In the current literature, the association between dairy intakes and body composition of children is controversial [32]. Indeed, results from a systematic review and a meta-analysis showed no significant association between dairy intakes and adiposity measures in pre-school- and school-aged children, although a modest protective effect of dairy consumption on adiposity measurements was found in adolescents [33]. Similarly, results from a systematic review of randomized controlled trials concluded that there were no significant associations between dairy consumption and body composition among children and adolescents [34]. The inconsistent association between dairy consumption and body composition could be explained by the fact that results vary according to various factors including the type of dairy products (i.e., low- vs. high fat) and amount consumed, age of children as well as their health status [32]. Further investigation is needed to understand the role of dairy products consumption on adipose tissue distribution among high-risk children such as those exposed in utero to GDM.

Finally, results of this study showed that scores related to whole fruits, dark green or orange vegetables and unsaturated fats were associated with a better anthropometric profile in GDM–, but not in GDM+ children. Indeed, a higher whole fruit score was associated with lower BMI z score, waist circumference, fat mass %, android and gynoid fat mass as well as with a lower android-to-gynoid fat mass ratio among GDM– children. The lack of association between the whole fruit score and anthropometric profile among GDM+ children could be explained in part by the fact that GDM+ children consumed significantly less whole fruits than GDM– children, which may have attenuated the potential effect of fruits consumption on children’s health. However, further investigation is needed to better understand this finding. Similarly, unsaturated fats score was associated with lower android, gynoid and total body fat mass percentage as well as lower android-to-gynoid fat mass ratio in GDM– children only. The absence of association in the GDM+ group compared to GDM– group could be explained by the type of food containing unsaturated fats and consumed by these children that could be different between groups. In fact, as shown by Joyce et al. in a cohort study of children from 5 to 12 years, sources of monounsaturated and polyunsaturated fats in children's diet come from a variety of foods with different nutritional content, such as fish and fried potatoes [35]. Thus, nutritional matrix of these different sources of unsaturated fat could influence differently children's health. However, this hypothesis needs to be confirmed.

It seems that we observed stronger associations between diet quality and the anthropometric profile than with the glycemic profile. This could be explained by the young age of participants included in our study. In fact, results from a study conducted among offspring of women with preexisting diabetes or GDM showed that only a small proportion of children presented an impaired glucose tolerance (IGT) before 10 years of age (1.2% in children <5 years and 5.4% in children aged 5–9 years), while the prevalence of IGT reached 19.3% in children aged between 10 and 16 years[36]. Thus, further studies should evaluate the association between diet quality and glycemic profile of older GDM+ children in order to better understand this relation.

Although this study highlights the importance of a healthy diet to prevent anthropometric and glycemic alterations in GDM+ and GDM– children, we cannot exclude the possibility that the association between a healthy diet and children's health could be mediated by other lifestyle habits, like physical activity [37] or maternal characteristics (BMI, education level). In fact, one limitation of this study is that physical activity has not been included in the analyses, given the limited number of participants that had complete data for this variable. Another limitation of the study is the small number of participants in the control group which limits the comparison between groups. Also, given the difficulty to recruit a large number of participants from a specific population such as children exposed in utero to GDM, participants included in this study had a wide range of ages (i.e., from 2 to 14 years) although the majority were within 2 and 9 years of age. However, adjustment for children's age were made in order to minimize the impact of this limitation. Finally, these results cannot be extended to the general population given that our sample of participants included mostly

Caucasians from high-income families. All analyses should be replicated in a larger cohort study in order to confirm associations observed in the present study.

On the other hand, our study presents several strengths. First, this is to our knowledge the first study to evaluate the association between diet quality and anthropometric and glycemic profiles of GDM+ children, a specific population at high risk of obesity and type 2 diabetes[2,3,5]. Given the lack of effective strategy to prevent these complications in this population, our study addresses the gap observed in the current literature. In addition, while a day-to-day variation in dietary intakes linked to 24HDR is possible, the use of two 24HDR questionnaires to assess children's diet reduced this daily variability in dietary intakes while minimizing burden in participants. Finally, the diet quality of children was evaluated using a score that has been validated in the Canadian population aged 2 years or more [13]. The use of a score to assess diet quality is a strong aspect of our study because it reflects a real-life context where foods are not consumed in isolation and can, therefore, have a synergistic effect on children's health.

Conclusion

In conclusion, our study showed that a healthy diet is associated with lower anthropometric and glycemic alterations in predisposed children born from mothers with GDM. Particularly, the total HEI-C score was associated with lower prevalence of overweight or obesity and a better adipose tissue distribution profile in GDM+ children. Given that GDM+ children are at high risk of obesity and type 2 diabetes later in life and that few children reached a good quality diet, the importance of adopting a healthy diet should be promoted early in their life in order to prevent metabolic alterations in this high-risk population.

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Tables

Table 8. 1 Participant's characteristics.

Characteristics	Mean ± SD or n (%)		
	GDM+ n= 104	**GDM- n= 38**	**p value**
Demographic			
Age (years)	6.0±2.5	6.8±2.3	**0.03**
2-5 (years)	53 (51.0)	12 (31.6)	0.12
6-9 (years)	41 (39.4)	21 (55.3)	
10-14 (years)	10 (9.6)	5 (13.2)	
Sex			
Boys	53 (51)	16 (42)	0.35
Girls	51 (49)	22 (58)	
BMI Z score	0.25±1.1	0.05±0.8	0.22
Overweight or obese	16 (15.4)	3 (7.9)	0.12
Waist circumference	55.9±7.8	54.9±5.9	**0.007***
Fat mass (%)[1]	27.0±6.4	24.7±4.0	**0.02***
Android fat mass (%)[1]	20.3±9.4	16.7±6.0	**0.01***
Gynoid fat mass (%)[1]	32.1±7.1	29.5±4.8	**0.03***
Android-to-gynoid fat mass ratio[1]	0.61±0.2	0.56±0.1	**0.03***
Glycemia (mmol/L) [2]	4.9±0.5	4.8±0.4	0.27*
Insulinemia (pmol/L) [2]	65.0±31.9	56.4±19.7	**0.02***
HbA1C (%)[3]	5.3±0.3	5.2±0.2	0.39*
HOMA-IR[4]	2.1±1.3	1.8±0.7	**0.03***
Maternal age (years)	38.1±4.8	36.2±5.4	**0.05**
Actual maternal BMI (kg/m^2)	26.8±6.6	23.9±4.1	**0.006**
GDM treatment during pregnancy[5]			
Diet	35 (37.6)	-	-
Medication (insulin or oral hypoglycemic agents)	58 (62.4)	-	
Family income (CAD$/year)[6]			
0 – 39 000	11 (13.3)	7 (22.6)	0.41
40 000 – 79 000	24 (28.9)	9 (29.0)	
80 000- 99 999	21 (25.3)	4 (12.9)	
>100 000	27 (32.5)	11 (35.5)	
Maternal education level[7]			
High school or less	17 (18.5)	4 (12.5)	0.71
College	18 (19.6)	6 (18.8)	
University	57 (62.0)	22 (68.8)	
Parity	2.2±0.8	2.2±0.8	0.79

[1]n=56 for GDM+ and n=30 for GDM-, [2]n=94 for GDM+ and n=33 for GDM-, [3]n=93 for GDM+ and n=34 for GDM-, [4]n=94 for GDM+ and n=32 for GDM-, [5]n=93, [6]n=83 for GDM+ and n=31 for GDM-, [7]n=92 for GDM+ and n=32 for GDM-. BMI: body mass index. * ANOVA adjusted for children's age and sex.

Table 8. 2 Diet quality during childhood.

	Mean ± SD or n (%)		
	GDM+ **n= 104**	**GDM-** **n= 38**	**p value**
HEI-C score			
Total score	68.4 ± 11.7	70.9 ± 11.1	0.25
Poor diet (score <50)	7 (6.7)	1 (2.6)	0.61
Diet that required improvement (≥50 score ≤80)	76 (73.1)	28 (73.7)	
Good quality diet (score >80)	21 (20.2)	9 (23.7)	
Mean intake of each component[ǂ]			
Total vegetables and fruit (serving/day)	4.7±2.5	5.4±2.6	0.06
Whole fruit (serving/day)	1.7±1.2	2.2±1.6	**0.01**
Dark green and orange vegetables (serving/day)	0.9±0.8	0.8±0.8	0.40
Total grain products (serving/day)	4.3±2.0	5.0±1.7	**0.04**
Whole grains (serving/day)	1.2±1.2	1.5±1.5	0.24
Milk and alternatives (serving/day)	2.3±1.2	2.4±1.1	0.41
Meat and alternatives (serving/day)	1.7±0.9	1.4±0.7	**0.03**
Unsaturated fats (g/day)	31.4±11.6	32.2±11.7	0.68
Saturated fats (g/day)	12.5±2.9	11.2±2.8	**0.03**
Sodium (mg/day)	2398±726	2436±816	0.76
Other food (% of energy intake/day)	21.8±11.5	21.5±9.6	0.91

[ǂ]Adjustment for children's age and sex. HEI-C: Canadian version of the American Healthy Eating Index.

Table 8. 3 Association between diet quality and anthropometric profile of GDM+ and GDM- children.

	GDM+ children						GDM- children					
	BMI Z score	Waist circum-ference[ǂ]	Fat mass %[ǂ, a]	Android fat mass (%)[ǂ, a]	Gynoid fat mass (%)[ǂ, a]	Android-to-gynoid fat mass ratio[ǂ, a]	BMI Z score	Waist circum-ference[ǂ, b]	Fat mass %[ǂ, b]	Android fat mass (%)[ǂ, b]	Gynoid fat mass (%)[ǂ, b]	Android-to-gynoid fat mass ratio[ǂ, b]
HEI-C score	0.01	-0.06	-0.07	-0.23	-0.07	-0.29*	-0.25	0.02	-0.25	-0.21	-0.24	-0.20
Adequacy scores												
Total vegetables and fruit	0.17	0.08	0.16	0.07	0.17	-0.02	-0.16	-0.15	0.26	0.24	0.27	0.18
Whole fruit	0.06	-0.009	0.07	0.08	0.12	-0.02	-0.50**	-0.44**	-0.39*	-0.46*	-0.38*	-0.41*
Dark green and orange vegetables	0.02	-0.02	-0.10	-0.16	-0.10	-0.23	-0.43**	-0.19	-0.11	-0.12	-0.14	-0.20
Total grain products	-0.21*	-0.14	-0.10	-0.35**	-0.21	-0.36**	-0.12	-0.11	-0.35	-0.30	-0.43*	-0.19
Whole grains	0.06	0.03	-0.15	-0.22	-0.14	-0.26	-0.17	0.08	-0.31	-0.21	-0.41*	-0.07
Milk and alternatives	-0.13	0.11	-0.15	-0.26	-0.14	-0.28*	0.11	0.13	-0.13	-0.24	-0.11	-0.23
Meat and alternatives	0.03	0.009	-0.001	-0.08	-0.09	-0.10	0.12	0.12	0.11	0.08	-0.07	0.15
Unsaturated fats	0.05	0.20*	0.16	0.09	0.16	0.10	0.002	-0.06	-0.43*	-0.44*	-0.44*	-0.40*
Moderation scores												
Saturated fats	-0.02	-0.10	0.22	0.17	0.20	0.14	-0.02	0.23	0.18	0.27	0.16	0.31
Sodium	-0.08	-0.24*	-0.26	-0.18	-0.15	-0.21	0.07	0.11	0.17	0.20	0.11	0.20
"Other food"	0.01	-0.05	-0.14	-0.24	-0.15	-0.20	-0.03	-0.01	-0.13	-0.20	-0.10	-0.24

Values are spearman's rank coefficient of correlation. *p<0.05, **p<0.01. [ǂ]Adjustment for children's age and sex. [a]n=56, [b]n=30

Table 8. 4 Association between diet quality and glycemic profile of GDM+ and GDM- children.

	GDM+ children				GDM- children			
	Glycemia[ǂ, a]	Insulinemia[ǂ, a]	HOMA-IR[ǂ, a]	HbA_{1c}[ǂ, b]	Glycemia[ǂ, c]	Insulinemia[ǂ, c]	HOMA-IR[ǂ, d]	HbA_{1c}[ǂ, e]
HEI-C score	-0.11	-0.22*	-0.22*	-0.18	-0.07	0.007	0.03	0.22
Adequacy scores								
Total vegetables and fruit	0.09	-0.03	-0.02	-0.06	0.19	0.24	0.29	0.15
Whole fruit	-0.06	-0.11	-0.10	0.05	-0.03	0.11	0.12	0.03
Dark green and orange vegetables	0.08	0.01	0.03	-0.13	0.13	<0.001	0.13	0.28
Total grain products	-0.07	-0.02	-0.03	-0.18	-0.009	-0.18	-0.08	0.11
Whole grains	0.06	-0.02	-0.02	-0.10	-0.05	0.33	0.27	0.29
Milk and alternatives	0.03	0.06	0.04	-0.10	-0.05	-0.06	-0.07	0.18
Meat and alternatives	-0.04	-0.007	0.003	-0.03	-0.44*	-0.30	-0.32	-0.11
Unsaturated fats	-0.08	-0.11	-0.12	-0.12	0.02	0.07	0.09	0.08
Moderation scores								
Saturated fats	0.15	-0.03	-0.003	0.02	0.13	0.08	0.10	0.13
Sodium	-0.15	-0.20	-0.19	0.16	-0.09	0.02	-0.09	-0.16
"Other food"	-0.10	-0.14	-0.15	-0.22*	-0.04	0.13	0.13	-0.16

Values are spearman's rank coefficient of correlation. *p<0.05, **p<0.01. [ǂ]Adjustment for children's age and sex. [a]n=94, [b]n=93, [c]n=33, [d]n=32, [e]n=34

Table 8. 5 Prevalence of being overweight or obese during childhood among GDM+ according to diet quality.

	Normal weight	**Overweight or obese**	**P value**
HEI-C score >70	47 (39.4)	3 (2.9)	**0.01**
HEI-C score ≤70	41 (45.2)	13 (12.5)	

Results are presented as following: n (%).

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Chapitre 9 Déterminants de la saine alimentation chez des enfants exposés et non exposés au diabète gestationnel

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L’article présenté dans ce chapitre s’intitule: *Determinants of Healthy Diet among Children Exposed and Unexposed to Gestational Diabetes*

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Résumé

Objectifs Évaluer l'association entre les déterminants individuels et environnementaux de la qualité alimentaire et la qualité de l'alimentation des enfants exposés (DG+) ou non-exposés (DG) au diabète gestationnel (DG); évaluer l'association entre les apports en fruits et légumes (FL) de la mère et ceux de son enfant.

Étude Transversale

Participants 142 enfants (104 DG+; 38 DG-) âgés de 6,2±2,5 ans

Variables La version canadienne du score de la qualité alimentaire *Healthy Eating Index* 2007 (HEI-C) et les apports en FL ont été obtenus par deux rappels alimentaires de 24h complétés avec les enfants. Pour les apports en FL de la mère, un questionnaire de fréquence alimentaire a été complété. Le poids et la taille ont été mesurés et un questionnaire sociodémographique a été administré.

Analyses Des modèles de régression linéaires ont été réalisés pour évaluer l'association entre les déterminants individuels et environnementaux et la qualité alimentaire des enfants selon le score HEI-C, avec une interaction pour le statut de DG.

Résultats Les repas pris en famille étaient associés au score HEI-C chez les enfants DG- mais pas chez les DG+ (ß= 9,97 et ß = -0,41, respectivement, p d'interaction=0,02). L'âge des enfants (ß = -1,45, 95%CI: -2,19, -0,72) et le niveau d'éducation de la mère (ß = 3,92, 95%CI: 0,35, 7,49) étaient associés au score HEI-C chez tous les enfants. Les apports en FL de la mère étaient associés positivement aux apports des enfants (r=0,30, p<0,001, r^2=0,09), avec une association plus prononcée chez les DG-.

Conclusion L'environnement alimentaire à la maison était associé différemment avec la qualité de l'alimentation selon le statut d'exposition au DG. Déterminer si cibler les repas pris en famille ou les apports en FL de la mère pourrait être une stratégie efficace afin d'améliorer l'alimentation

des enfants DG+ devrait être investigué dans de futures études.

Abstract

Objectives To evaluate the association between individual and environmental determinants of diet quality with diet quality of children exposed to gestational diabetes mellitus (GDM+) and unexposed (GDM-); to study the association between mother and child vegetables and fruit (VF) intakes.

Design Cross-sectional study

Participants One-Hundred and forty-two children (104 GDM+; 38 GDM-) aged 6.2 ± 2.5 years.

Variables Canadian Healthy Eating Index 2007 (HEI-C) and VF were obtained with two 24-hour dietary recall questionnaires in children. Maternal VF was obtained by a validated food frequency questionnaire. Weight and height were measured. Sociodemographic determinants were obtained by questionnaires.

Analysis Linear regression models were used to evaluate the association between individual and environmental determinants and the HEI-C score with interaction for GDM status.

Results Family meals were associated with HEI-C among GDM- but not GDM+ children (ß = 9.97 and ß = -0.41, respectively, p for interaction=0.02). Children's age (ß = -1.45, 95%CI: -2.19, -0.72) was a determinant of HEI-C among all children. Maternal VF intakes were positively associated with children's VF intake ($r=0.30$, $p<0.001$, $r^2=0.09$), with association of larger variance among GDM- children ($r = 0.38$, $r^2 = 0.14$, $p = 0.02$) than GDM+ children ($r = 0.23$, $r^2 = 0.05$, $p = 0.02$).

Conclusion The food environment at home was associated differently with the diet quality of GDM+ and GDM- children. Whether targeting family meals and maternal diet quality is a good strategy to improve children's diet quality among GDM+ children needs to be further investigated.

Title Page

Determinants of Healthy Diet among Children Exposed and Unexposed to Gestational Diabetes

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Background

Children born from mothers with a pregnancy complicated by gestational diabetes mellitus (GDM) are at high-risk of developing many health problems later in life, such as obesity and type 2 diabetes.[1, 2] Despite efforts made to prevent GDM, its prevalence has increased in the past decades, reaching almost 8% of the pregnancies in 2012 in Quebec City, Canada.[3] Hence, postnatal strategies to prevent complications among children exposed in utero to GDM are needed. Some studies highlighted that adopting a healthy diet in childhood was associated with better anthropometric and glycemic profiles in this population.[4, 5] A total of 20% of children born from mothers with GDM adopted a healthy diet according to the 2007 Canadian version of the healthy eating index (HEI-C) and 42% met the recommended intake of vegetable and fruits (VF) according to the Canada's Food Guide 2007, another indicator of diet quality in children.[4, 6] Furthermore, among GDM mothers, 57% adopted a healthy diet during the years following their pregnancy complicated by GDM.[7]

Many factors can influence the diet quality of children.[8, 9] Among them, longer breastfeeding duration during infancy has been associated with improved diet quality in children aged 3.5 years.[9] In addition, higher maternal education level has been associated with greater adherence to the Mediterranean diet in children, which also represent a diet of good quality.[10] Furthermore, food environment at home, such as accessibility to healthy foods as well as parent's diet quality both have an important impact on children's diet quality.[11] According to a systematic review conducted among children aged between 6 and 12 years, mothers are the predominant role model regarding VF intakes of their child, particularly with a positive association between maternal VF intakes and children's VF intakes.[11] Accordingly, studying the modeling role of mothers on children's diet quality is of particular interest among the GDM population. While the altered fetal environment in context of GDM is known to increase risk of obesity among exposed children, less is known regarding maternal influence on diet quality development in the postnatal period in this specific population. On one hand, it is possible that poor lifestyle habits in mothers, which is a risk factor for GDM development[12], could be transferred to the child later in life, resulting in a higher risk of developing obesity and metabolic complications. On the other hand, women with a pregnancy complicated by GDM may be aware of the risk for her and her child to develop metabolic abnormalities later in life[13], which could lead to the adoption of a healthy diet in the postnatal period for the whole family.

Thus, taken together, individual and environmental factors can have a major influence on the diet quality of children but there appears to be a lack of studies on this topic conducted among children exposed (GDM+) and unexposed (GDM-) to GDM in utero. Accordingly, aims of this study were 1) to examine the association between individual and environmental determinants of diet quality with diet quality of GDM+ and GDM- children and 2) to study whether maternal diet quality is associated with children's diet quality, using VF intakes as a proxy of diet quality, among GDM+ and GDM- children. This study will answer, in this specific population, the following questions: 1) Are individual and environmental factors associated with diet quality differently among GDM+ and GDM- children? 2) Is maternal diet quality associated with diet quality of their children in both groups?

Methods

Participants And Recruitment

Children aged between 2 and 14 years and born between 2003 and 2013 were recruited in a study that was previously described.[4,7] Briefly, invitation to participate in a study that aimed to investigate the impact of GDM on both maternal and children's health and to investigate the role of postnatal factors in these associations was sent to participants from a previous project conducted among women with prior GDM.[7] In addition, recruitment was conducted using medical records from the 2 major hospitals with a neonatal care unit in the area of Quebec City, administrative data from the provincial health plan registry (*Régie de l'assurance maladie du Québec*), as well as email addresses of student and employees of the Université Laval Community. Recruitment was conducted in Quebec City where the great majority of the population is non-Hispanic White, with 6% of visible minority.[14] GDM+ children had to be exposed in utero to GDM only, i.e. no other type of pre-existing diabetes (type 1 or type 2 diabetes). Diagnosis of GDM was confirmed for 91% of the participants and self-reported for the remaining 9%. The majority of children included (92%) were born before 2013, i.e. when GDM was diagnosed with 2003 criteria of Diabetes Canada15. Children from the comparison group (GDM-) had to be born from a mother without any history of diabetes, i.e. no GDM, type 1 or type 2 diabetes. The study took place at the Institute of Nutrition and Functional Foods (INAF) research center. Written consent was obtained from all participating mothers for their children and children's assent was also obtained after a detailed explanation of their implication in the study was made by the research assistant. Children provided assent to participate to the study by writing their initials (or name) on the assent form. Ethical approval was obtained from the Université Laval Ethics Committee (2011-196-A-4 R-3) and from the *Centre Hospitalier Universitaire de Québec* Ethics Committee (2015-2031). This study was registered in the Clinical Trials.gov registry (NCT01340924).

Procedures

Selection of potential determinants of diet quality was based on a model proposed by De Cosmi et al. regarding environmental factors that influenced child eating behaviors.[8] This model was informed by the social ecological model used in the Food Friends program, an intervention study that aimed to reduce obesity in early childhood.[16] In the present study, potential individual and environmental determinants that were available were selected. Individual factors, i.e. factors that are inherent to the child, were children's age and sex, birth weight, human milk feeding (total and exclusive), timing of solid food introduction and current body mass index (BMI) z-score at the time of the visit. Environmental factors, i.e. factors that are external to the child and are rather related to parents and family, were family income, maternal education level, family meals, meals taken while watching a screen, maternal perception of accessibility to healthy foods, current maternal BMI and number of siblings. Information regarding the school environment and ethnicity were not available and were not included in the present study.

Data Collection in Children

Individual Determinants. All participating children came to the research center for a single visit with their mother to complete questionnaires and tests. Children's age and sex were documented by mothers during the recruitment phone call and confirmed by questionnaire at the onsite visit. Children's age was given in term of years. Infant feeding practices, including duration of total and exclusive human milk feeding and the timing of solid food introduction, were retrospectively documented by a self-administered questionnaire completed by the mother. Data about whether human milk was expressed or directly from the breast were not available. Anthropometric measurements of children were taken in duplicate at the research center by a trained research assistant. Height was measured to the nearest 0.1 centimeter using a stadiometer, weight was measured to the nearest 0.1 kilogram using a calibrated balance (Tanita BC-418) and BMI was calculated (kg/m2).[17] Children's BMI z-score was calculated using World Health Organization Anthroplus software (version 1.0.4, WHO, Geneva, Switzerland, 2009). Finally, birth weight of children was obtained using the child health record.

Dietary intakes. Dietary intakes of children were assessed using 2 24-hour dietary recall questionnaires. Briefly, a first 24-hour dietary recall questionnaire was completed with a trained dietitian or a student in nutrition at the onsite visit using the validated multiple-pass method.[18] All food and liquid items consumed the previous day, from midnight to midnight, were listed. Three dimensional food models were used to enhance accuracy of portion size estimates. For children younger than 10 years, the 24-hour dietary recall questionnaire was completed with the mother and the child was asked to add information if needed, i.e. for food consumed outside of home.[19] For older children, the 24-hour dietary recall questionnaire was completed with the child, with the help of the mother if needed, i.e. for food preparation or recipes. The second 24-hour dietary recall questionnaire was conducted over the phone, using the same validated method, 7-10 days after the visit at the research center.

Diet quality of children was assessed using mean of intakes from the 2 24-hour dietary recall questionnaires to calculate the HEI-C score. The HEI-C score has been developed in the Canadian population, including children aged of 2 years or more, using data from the 2004 Canadian Community Health Survey – Nutrition.[20] This score is composed of 11 components, which include 3 moderation components, i.e. foods that should be limited in a healthy diet (saturated fats, sodium, and “other food”) and 8 adequacy components, i.e. food items that should be consumed in greater amounts in order to achieve a healthy diet (total VF, whole fruit, dark green and orange vegetables, total grain products, whole grains, milk and alternatives, meat and alternatives, and unsaturated fats).[20] The maximal possible score is 100, with moderation components contributing to 40 points and adequacy components to 60 points. In addition to the HEI-C score, intakes of VF were used as an indicator of diet quality to facilitate analysis of the association between diet quality of mother and her child. Mean intakes from the 2 24-hour dietary recall questionnaires were used to calculate servings of VF consumed per day according to the Canada’s Food Guide 2007.[21] Other nutritional components used to calculate the HEI-C score were extracted using the Nutrition Data System for Research software (NDSR version 2011, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA).

Data Collection in Mothers

Environmental Determinants. Mothers completed a self-administered questionnaire on socioeconomic and demographic data based on questionnaires used in large national surveys[22] where family income for the previous year, highest education levels completed by the mother and parity were obtained. Current maternal weight and height were measured using the same method as children and BMI was calculated.[23] Children's meal environment at home was assessed by a questionnaire, also based on questionnaires used in large national surveys[22], completed by the mother that included the following questions: 1) during the past 7 days, how many times the child ate his meal with family members? 2) during the past 7 days, how many times the child ate his meal in front or with a screen? Answers were given separately for breakfast (0-7 meals/week), lunch (0-7 meals/week) and diner (0-7 meals/week) and mean meals per day was calculated for family meals and meals consumed while watching a screen respectively. Finally, the validated Perceived Food Environment questionnaire was also completed by the mother and the score of perceived accessibility to healthy food was calculated.[24]

Maternal Dietary Intakes. Maternal dietary intakes were assessed using a validated food frequency questionnaire (FFQ) administered by a trained dietitian or a student in nutrition.[25] Briefly, food items and quantity consumed in the past month were compiled using a list of 91 items frequently consumed in the population of Quebec. Participants intakes were given in term of day (ex: 1 fruit per day), week (ex: 125 ml of fruit juice once per week) or month (ex: 1 cup of salad, 2 times in the last month). Three-dimensional food models were used to enhance accuracy of portion size estimates. Servings of VF were calculated according to the Canada's Food Guide 2007 and were presented as mean daily servings.[21]

Data Analysis

Participant characteristics were compared between GDM+ and GDM- groups using student t test, Chi-square test of independence (χ^2) or Fisher exact test. Assumptions for statistical analysis were tested and data transformation according to Box-Cox procedure was computed when needed. Multivariable regression models were computed for every individual and environmental determinant to estimate their potential association with diet quality of children (Model 1). Analyses for Model 1 included one predictor variable (each determinant (n=14)) and one outcome variable (HEI-C score). Adjustment for children's sex was made in the model assessing the association between children's age and diet quality. In the model assessing the association between children's sex and diet quality, adjustment for children's age was made. Adjustment for children's age and sex were performed in all other models. Interaction with GDM status was tested in these models to verify whether determinants of children's diet quality vary according to in utero exposure to GDM. In addition, a multivariable model including all potential determinants of diet quality entered simultaneously in the model (except for exclusive human milk feeding duration) was computed to minimize possible influence of other determinants in the association with the diet quality (Model 2). The exclusion of exclusive human milk feeding duration in Model 2 was based on multicollinearity analyses that showed a moderate correlation between this cofactor and total human milk feeding duration (r^2=0.61, p<0.0001) and the timing of solid food introduction (r^2=0.60, p<0.0001). Thus, Model 2 included 13 predictor variables and one outcome (HEI-C score).

Dietary intakes of mothers and children were assessed using different dietary assessment instruments, namely a FFQ and 2 24-hour dietary recall questionnaires, respectively. Dietary intakes data measured using a 24-hour dietary recall questionnaire are mainly influenced by within-individual random errors that is not the case for the FFQ.[26] To increase comparability between dietary assessment methods and compare usual VF intakes of the mothers to usual VF intakes of the children, within-individual random errors of the 24-hour dietary recall questionnaire were corrected using regression calibration and the National Cancer Institute method.[27] This method was not applicable to the HEI-C score that included many components, explaining why VF intakes were used as a proxy of diet quality for mothers and children. Covariates of the regression calibration model were children's age and sex. Spearman correlation between maternal VF intakes and children's usual VF intakes was computed using dietary intakes data calibrated using the National Cancer Institute method.[27]

Post-hoc power calculation using G*power software (version 3.1.9.6, Kiel University, Germany, 1992-2020) was computed using current sample size and parameter estimates derived from data from this paper (Model 2) and a statistical power of 98% was obtained. A p value under 0.05 was considered significant although in Model 1, a p value of 0.004 was considered significant after considering Bonferroni correction for multiple comparisons. The statistical software SAS studio v3.8 (2020) was used to compute analyses. Figures were made in R version 4.0.2 (2020).

Results

A total of 142 children (n = 104 GDM+ and n = 38 GDM-) were included in this study. Characteristics of the participants presented as individual and environmental determinants of diet quality are shown in **Table 1**. The mean age of children was 6.2 ± 2.5 years, with 46% of them aged between 2 and 5 years, 44% aged between 6 and 9 years, and 10% aged between 10 and 14 years, with 2 of them aged > 12 years. Among GDM+ women, 62% used medication during pregnancy to control their diabetes (either insulin or oral hypoglycemic agent), whereas the remaining 38% controlled their hyperglycemia with diet. The total HEI-C score was 69.1 ± 11.6 in all children (n = 142) and was similar between GDM+ and GDM- children (68.4 ± 11.7 and 70.9 ± 11.1, P = 0.25, respectively, **Table 2**).

Among individual determinants of diet quality in the entire sample, for every increase of 1 year in children's age, HEI-C score decreased 1.45 unit (β = -1.45; 95% confidence interval [CI], -2.19 to -0.72; P = 0.0001; **Table 3**). For environmental determinants, we observed that maternal BMI was negatively associated with HEI-C score (β = -0.42, 95% CI, -0.71 to -0.14, P = 0.004, Table 3). Results that included all individual and environmental determinants in the regression model (Model 2) presented similar results.

Some individual and environmental determinants of the diet quality were different according to GDM exposure (**Table 3**). Being part of a family with income > $80 000 (CAD$/y), compared with lower income, was associated with higher HEI-C score in GDM- but not in GDM+ children (β = 6.53; 95% CI, -0.35 to 13.4; P = 0.06 and β = -2.75; 95% CI, -7.05 to 1.56; P = 0.21, respectively; P for interaction = 0.03). Furthermore, family meals were positively associated with HEI-C score of GDM- children, whereas the association with diet quality of GDM+ children was of small magnitude (β = 9.97; 95% CI, 2.4−17.5; P = 0.01 and b = -0.41; 95% CI, -4.41 to 3.59; P = 0.84, respectively; P for interaction = 0.02), suggesting that the family environment influences children diet quality according to GDM exposure.

Finally, the association between mother and child diet quality was studied. As shown in **Figure 1**, the distribution of usual VF intakes differed between GDM+ and GDM- children, with differences more pronounced at higher percentiles of consumption. Among GDM- children, VF intakes were greater by 1.3 servings per day at the 95th percentile of consumption ($P = 0.02$), by 1.1 servings at the 85th percentile ($P = 0.03$), and by 0.9 serving at the 75th percentile ($P = 0.05$). Mother's VF intakes were associated with children's VF intakes in the entire sample ($r = 0.30$, $r^2 = 0.09$, $P = 0.0003$, **Figure 2, A**). At lower maternal VF intakes (ie, < 5 servings/d), maternal VF intakes had a linear association with VF intakes of children. However, as shown in **Figures 2, A and B**, this association had an apparent ceiling effect > 5 servings of maternal VF intakes (ie, an increase in maternal VF intakes was no longer reflected by increased children's VF intakes after 5 servings/d). Furthermore, intakes of VF among GDM- children seemed to be associated with their mother's intakes in a greater manner than GDM+ children ($r = 0.38$, $r^2 = 0.14$, $P = 0.02$ and $r = 0.23$, $r^2 = 0.05$, $P = 0.02$, respectively, **Figure 2, B**).

Discussion

In this study, the diet quality of GDM + and GDM- children was similar between groups according to the HEI-C score and was comparable to the Canadian population.[20] Results also showed that some environmental factors were associated differently with diet quality depending on in utero exposure to GDM. For example, this study highlighted that family meals were associated differently with diet quality between GDM+ and GDM- children, even if the mean number of family meals was similar between groups. Comparison with existing literature is limited, but 1 study evaluated the association between exposure to GDM and child's feeding practices and found no difference regarding maternal feeding style on their children (ie, restriction or pressure to eat).[28] Results of this previous study conducted by Martin et al[28] also highlighted the fact that women with a history of GDM were not more concerned about their child's weight than women without previous GDM, suggesting that these mothers may not be aware of the higher risk of obesity for their child.[28] This is in accordance with results from a qualitative study conducted in a small group of GDM mothers of children aged 3−4 years in which the majority of them reported neither being aware of the increased risk of obesity for their children nor of dietary recommendations for them.[29] Thus, they may not modify their lifestyle habits to minimize this risk. Accordingly, it is possible that women without a history of GDM had better dietary habits than women with previous GDM, which could result in a greater influence on children's diet quality during family meals. As demonstrated in this study, GDM+ women and their children consumed less VF than the GDM- group, which supports this hypothesis.

In the same line, this study showed that mothers' VF intakes were associated with children's VF intakes in the entire sample, and this association seemed to differ according to GDM status, with the association accounting for larger variance among GDM- than GDM+ children. The association between maternal and child's VF intakes in the general population has been demonstrated previously.[30–33] For example, in a study conducted by Robinson et al[30] in an Australian population, positive correlations in mother and child dyad for vegetable intakes ($r = 0.40$, $P = 0.01$) and for fruit intakes ($r = 0.47$, $P < 0.0001$) were observed.[30] This association could be explained by the fact that mothers may be role models regarding their children's dietary intakes.[34] Furthermore, the fact that parents control the availability of food at home could explain the similarity between their diet composition.[11] However, the weak to moderate correlation ($r = 0.30$, $r^2 = 0.09$) found in this study suggests that maternal dietary intakes are not the only factor contributing to children's VF intakes.

Family income was not associated with the diet quality of children in the entire cohort but was associated with a greater HEI-C in GDM- but not in GDM+ children. This latter result among GDM+ children is not in accordance with results from the current literature showing a positive association between family income and diet quality.[35,36] It is well established that food with higher energy density, and lower quality was generally less expensive and consumed more among groups of lower socioeconomic status.[37] In contrast, a family with greater revenue may have less time for planning meals and cooking if both parents are working full-time[38], which may result in a diet of lower quality even with higher revenue.

Finally, in all children, age was negatively associated with diet quality, according to several studies.[20,39] The association between being older and having a lower quality diet can be explained by the fact that as a child grows, parents have less control over their child's dietary intake, especially outside the home. Given that food preferences are known to drive food choices of children,[40] this could result in the consumption of more fatty and sugary foods, generally preferred by children, and fewer vegetables that are generally disliked by children.[41,42]

This study presents some limitations. First, the small number of GDM- children may have limited the comparison of results between groups. Therefore, results should be interpreted with caution and considered exploratory. Second, no information regarding the food environment outside the home (ie, at daycare, school, summer camp, etc) was available in this study. However, data collection was completed during the summer vacation for 90% of children, which limits the potential impact of the school environment on children's diet for this study period. In contrast, the fact the study was conducted during the summer school break could also affect some of the environmental determinants, such as the number of family meals. In addition, questions regarding family meals and meals taken while watching a screen were not mutually exclusive, which could have impacted the association between family meals and the diet quality of children.

Furthermore, data on fathers and other caregivers would have been relevant to have a complete profile of the food environment, although it is well established that mothers have a greater influence on their children's dietary intakes than fathers.[11] The use of 2 different tools to assess dietary intake of mothers and children is another limitation of this study, although the analysis of the association between maternal diet quality and children's diet quality has been conducted using statistical methods that considered different measurement errors related to the different methods of dietary assessment used for mothers (FFQ) and children (24- hour dietary recall questionnaire). Furthermore, infant feeding practices were evaluated using a non validated questionnaire. Finally, results cannot be generalized to other populations given that participants were mostly non-Hispanic White with high income and education levels and given that GDM women had adequate glycemic control during pregnancy, as suggested by similar birth weight between the 2 groups.

Conclusion

In conclusion, the results of this study highlighted individual and environmental determinants that were associated with the diet quality of children, with some of them that were associated differently according to GDM status. The fact that family meals were associated differently with diet quality among GDM+ and GDM- children, even if the number of family meals per day was similar between groups, may be a result of healthier lifestyle habits among GDM- women that are transmitted to their children during mealtime. The higher BMI and the lower consumption of VF among GDM+ women than GDM- women, could be a factor explaining this result and needs further investigations. Thus, future intervention studies in this population at high risk of obesity using environmental determinants identified in the current study are needed to better understand their role in diet quality development among GDM+ children. Whether improving the diet quality of mothers and the food environment at home is a good strategy to improve children's diet quality among GDM+ children needs to be further investigated in a larger study with diverse sociodemographic characteristics.

Tables

Table 9. 1 Individual and Environmental Determinants of Diet quality in Childhood among GDM+ and GDM- Children (N=142)

	Mean ± SD or n (%)						
	All children		**GDM+**		**GDM-**		
	N=142	Range (min- max)	**n= 104**	Range (min- max)	**n= 38**	Range (min- max)	**P value**
Individual determinants							
Age (years)	6.2±2.5	2.0 – 14.0	6.0±2.5	2.0 - 14.0	6.8±2.3	3.0 – 11.0	0.03
Sex							
Boys	69 (49)		53 (51)		16 (42)		0.35
Girls	73 (51)		51 (49)		22 (58)		
Current BMI Z score	0.2±1.0	-2.2 – 3.8	0.25±1.1	-2.2 – 3.8	0.05±0.8	-1.4 – 2.0	0.22
Birth weight (kg)	3.3±0.5	2.3 – 5.1	3.38±0.46	2.3 – 4.3	3.25±0.53	2.3 – 5.1	0.17
Total human milk feeding duration (months)	9.3±7.2	0.1 – 38.0	8.8±7.3	0.1 – 38.0	10.6±6.6	0.5 – 36.0	0.07
Exclusive human milk feeding duration (months)	4.3±1.7	0.1 – 7.0	4.1±1.8	0.1 – 7.0	4.8±1.4	1.0 – 7.0	0.06
Timing of solid food introduction (months)	5.0±1.2	1.0 – 7.0	4.9±1.2	1.0 – 7.0	5.3±1.2	1.0 – 7.0	0.16
Environmental determinants							
Family income (CAD$/year)							
0 – 39 000	18 (16)		11 (13)		7 (23)		0.41
40 000 – 79 000	33 (29)		24 (29)		9 (29)		

80 000- 99 999	25 (22)		21 (25)		4 (13)		
>100 000	38 (33)		27 (33)		11 (36)		
Maternal education level							
High school or less	21 (17)		17 (19)		4 (13)		0.71
College	24 (19)		18 (20)		6 (19)		
University	79 (64)		57 (62)		22 (69)		
Current maternal BMI (kg/m^2)	26.0±6.2	16.8 – 50.3	26.8±6.6	16.8 – 50.3	23.9±4.1	17.1 – 36.3	0.006
Parity	2.2±0.8	1.0 – 4.0	2.2±0.8	1.0 – 4.0	2.2±0.8	1.0 – 4.0	0.79
Maternal perception of accessibility to healthy foods score (out of 5)[1]	4.0±0.5	1.3 – 4.8	4.0±0.5	2.2 – 4.8	4.0±0.6	1.3 – 4.7	0.75
Family meals/day[2]	2.4±0.5	0 - 3	2.4±0.5	0 - 3	2.4±0.5	1 - 3	0.81*
Meal consumed while watching a screen/day[3]	0.5±0.7	0 - 3	0.5±0.7	0 - 3	0.5±0.6	0 – 2.3	0.45*

GDM: Gestational diabetes mellitus. GDM+: children exposed to GDM *in utero*. GDM-: children unexposed to GDM *in utero*. BMI: body mass index. Results are expressed as mean ± standard deviation or n (%) and were compared between GDM+ and GDM- using Student t-test, chi-square test of independence or Fisher exact test. *Adjustment for children's age and sex.[1]n=98 for GDM+ and n=35 for GDM-; [2]n=101 for GDM+; [3]n=95 for GDM+ and n=37 for GDM-.

Tableau 9. 2 Diet Quality of Mothers and Children in GDM+ and GDM- Groups

	Mean ± SD			
	All children N=142	**GDM+ n= 104**	**GDM- n= 38**	**p value**
Diet quality of children				
HEI-C score	69.1±11.6	68.4±11.7	70.9±11.1	0.25
VF (serving/day)	4.9±2.5	4.7±2.5	5.4±2.6	**0.08***
Fruit (serving/day)	2.8±1.9	2.6±1.9	3.2±1.7	**0.02***
Vegetable (serving/day)	2.1±1.5	2.1±1.5	2.2±1.5	0.79*
VF according to children's age				
VF (serving/day) among 2-5 years[1]	4.5±1.9	4.3±1.8	5.2±1.9	0.30**
VF (serving/day) among 6-9 years[2]	5.3±3.0	5.2±3.2	5.5±2.6	
VF (serving/day) among 10-14 years[3]	4.8±2.7	4.3±1.9	5.8±4.1	
Diet quality of mothers				
Maternal consumption of VF (serving/day)	7.4±2.9	6.9±2.8	8.7±3.0	**0.001**
Maternal fruit intakes (serving/day)	2.8±1.7	2.6±1.5	3.4±2.0	**0.03**
Maternal vegetable intakes (serving/day)	4.6±2.1	4.4±2.1	5.4±2.0	**0.01**

GDM+: group of mothers with previous GDM and their child exposed *in utero*. GDM-: group of mothers without previous GDM and their child. HEI-C: Healthy Eating Index adapted for a Canadian population; VF: Fruit and vegetable. *ANOVA adjusted for children's age and sex. **Results from a 6 groups ANOVA adjusted for multiple comparisons. [1]n=53 for GDM+ and n=12 for GDM-; [2]n=41 for GDM+ and n=21 for GDM-; [3]n=10 for GDM+ and n=5 for GDM-.

Tableau 9. 3 Association Between Individual and Environmental Factors and the HEI-C score in all Children

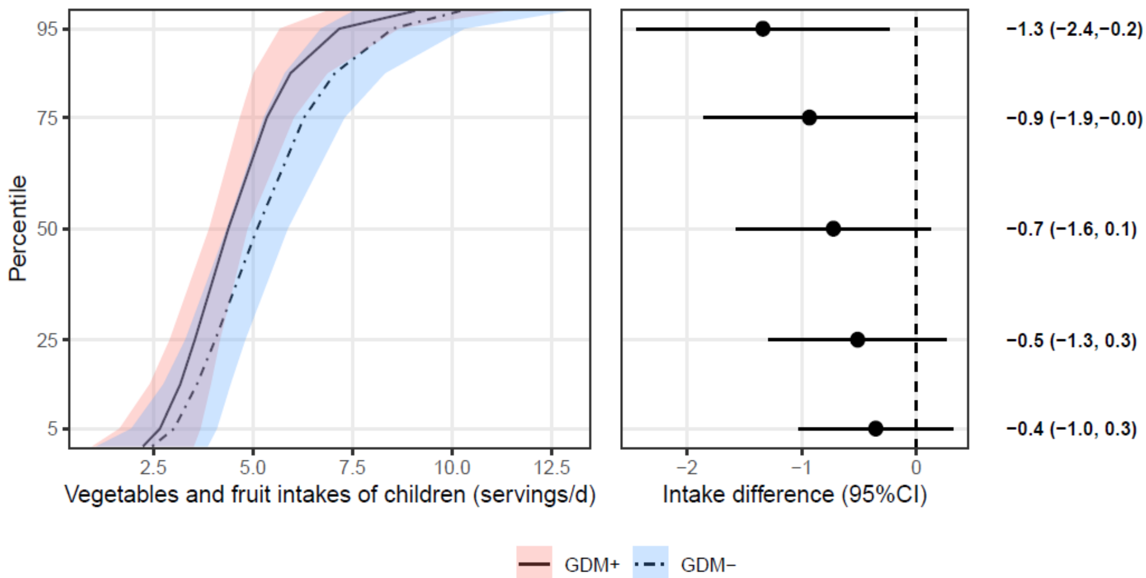
Determinants	Model 1[1]					Model 2[2]			
	Beta	P value*	95% CI		*P interaction with GDM status*	Beta	P value	95% CI	
Individual determinants									
Children’s age	**-1.45**	**0.0001**	**-2.19**	**-0.72**	0.62	**-1.59**	**0.0002**	**-2.42**	**-0.76**
Boys	1.48	0.42	-2.13	5.09	0.24	1.93	0.35	-2.16	6.02
Birth weight	-0.20	0.92	-4.05	3.66	0.44	1.61	0.46	-2.64	5.86
Age at solid food introduction	1.20	0.15	-0.41	2.82	0.15	-0.001	0.99	-1.84	1.83
Total human milk feeding duration	0.06	0.64	-0.20	0.33	0.21	0.03	0.83	-0.26	0.33
Exclusive human milk feeding duration	0.26	0.67	-0.92	1.44	0.52	-	-	-	-
BMI Z score	-0.68	0.46	-2.49	1.14	0.39	-0.002	0.99	-2.29	2.28
Environmental determinants									
Family income ≥ 80 000$/year (Reference < 79 999$/year)	-0.18	0.92	-3.87	3.51	**0.03**	-2.13	0.41	-7.18	2.92
Mother with a University degree (Reference education levels less than University)	3.92	0.03	0.35	7.49	0.53	3.18	0.19	-1.61	7.98
Family meals per day[4]	1.87	0.31	-1.75	5.48	**0.02**	1.85	0.39	-2.33	6.02

Meals taken while watching a screen per day[5]	0.55	0.70	-2.23	3.33	0.41	2.46	0.18	-1.13	6.05
Maternal BMI	**-0.42**	**0.004**	**-0.71**	**-0.14**	0.62	-0.92	0.02	-0.10	5.95
Parity	-1.53	0.21	-3.92	0.87	0.41	-1.97	0.19	-4.92	0.97
Maternal perception of accessibility to healthy foods score[6]	0.34	0.86	-3.29	3.96	0.36	-0.68	0.72	-4.43	3.05

GDM: gestational diabetes. BMI: body mass index. Results are expressed as beta coefficient of multivariable regression models. *According to Bonferroni correction for multiple comparisons, p values under 0.004 are considered significant. [1]Adjusted for children's age and sex, when appropriate. [2]All characteristics were entered simultaneously into the multivariable model except for exclusive breastfeeding duration. [3]Interaction between GDM status, determinants and diet quality were computed in Model 1 for every determinant. [4]n=101 for GDM+; [5]n=95 for GDM+ and n=37 for GDM-,[6]n=98 for GDM+ and n=35 for GDM-.

Figures

Figure 9. 1 Distribution of Usual Intakes of Vegetables and Fruit According to Exposure to GDM in utero

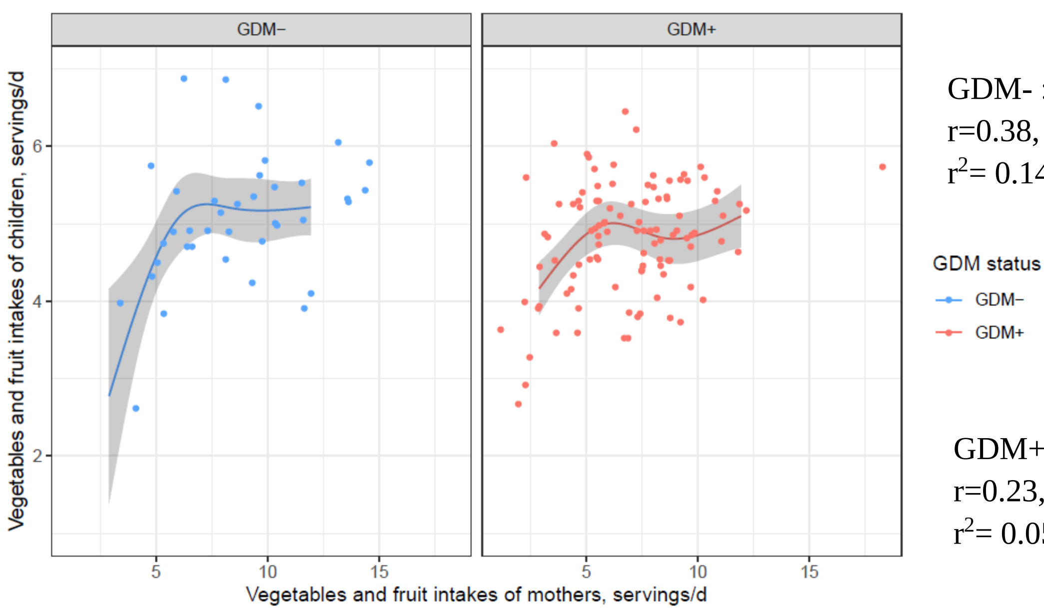


GDM+: exposed to gestational diabetes mellitus, GDM-: unexposed to gestational diabetes mellitus. Intake difference is represented as mean difference of usual vegetable and fruit servings/day between GDM+ and GDM- children, with 95% confident intervals.

Figure 9. 2 Association Between Maternal Vegetable and Fruit Intake and Children's Usual Vegetable and Fruit Intake

r=0.30, r^2= 0.09, p<0.001

a) Association Between Maternal Vegetable and Fruit Intake and Children's Usual Vegetable and Fruit Intake using Spearman Correlation in the Entire Sample.



GDM- :
r=0.38,
r^2= 0.14, p=0.02

GDM+ :
r=0.23,
r^2= 0.05, p=0.02

b) Association Between Maternal Vegetable and Fruit Intake and Children's Usual Vegetable and Fruit Intake According to Gestational Diabetes Mellitus Exposure. GDM+: group of mothers with previous GDM and their child exposed in utero. GDM-: group of mothers without previous GDM and their child.

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Discussion et conclusion

Les enfants ayant été exposés au DG *in utero* présentent un risque élevé d'obésité et de DT2 plus tard dans la vie et à ce jour, peu de stratégies de prévention de ces complications ont été identifiées dans la période postnatale.[118] Dans le but d'offrir une meilleure qualité de vie à ces enfants à plus long terme, il devient alors nécessaire d'identifier de telles stratégies. C'est dans cette optique que l'objectif général de cette thèse de doctorat a été établi, c'est-à-dire d'évaluer l'association entre l'alimentation de l'enfant et la prévention des complications associées à une exposition intra-utérine au DG.

Retour sur les principaux résultats

Tout d'abord, les résultats de ce projet de doctorat ont permis de déterminer que l'alimentation en bas âge pourrait influencer le développement des préférences ou des habitudes alimentaires des enfants à plus long terme. En effet, tel que présenté au chapitre 7, l'introduction des jus de fruits à 100% pur avant l'âge de neuf mois était associée à une plus grande consommation de jus de fruits pendant l'enfance chez les enfants ayant été exposés au DG *in utero*. Une tendance à une plus grande consommation de boissons artificiellement sucrées pendant l'enfance a aussi pu être observée chez les enfants exposés au DG et ayant reçu du jus de fruits de façon précoce, mais le faible nombre d'enfants consommant des boissons sucrées a probablement contribué au manque de puissance statistique permettant d'observer une association franche. Ces résultats sont en accord avec l'hypothèse selon laquelle l'introduction d'aliments au goût très sucré en bas âge, dans une période critique du développement, pourrait entrainer une préférence pour ces mêmes aliments plus tard dans la vie, qui se traduirait par une plus grande consommation de ce ceux-ci.[153] Cependant, contrairement à notre hypothèse initiale, la consommation de desserts et de sucreries n'était pas plus grande chez les enfants ayant été exposés au jus de façon précoce. Il n'est pas clair si la matrice alimentaire pourrait influencer le développement des préférences alimentaires et donc expliquer ce résultat inattendu. En effet, comme les aliments liquides diffusent plus facilement leur saveur dans la cavité orale que les aliments solides, la matrice alimentaire pourrait influencer la perception des saveurs chez l'individu.[214] Cependant, il est possible de penser que le fait d'introduire du jus tôt dans l'alimentation de l'enfant pourrait entrainer une habitude à consommer ce type de boisson, ou encore que les parents qui en offrent à leurs enfants avant l'âge d'un an continueraient à en offrir tout au long de l'enfance, comme il a été observé dans d'autres études.[166, 168] Somme toute, les résultats de l'étude portant sur l'introduction des jus ont souligné l'importance d'établir de saines habitudes alimentaires tôt dans la vie de l'enfant. Cette conclusion concorde avec les études démontrant que les habitudes alimentaires établies en bas âge sont généralement maintenues pendant l'enfance et l'adolescence.[8] Ainsi, éviter de donner du jus de fruits aux jeunes enfants pourrait aider à prévenir le développement d'une préférence pour les aliments sucrés ou encore l'habitude de consommer ce type de boissons plus tard dans la vie. De l'éducation auprès des parents devrait être faite afin de les sensibiliser à l'impact potentiel de la consommation de jus de fruits en bas âge chez leur enfant et ce, principalement chez les enfants ayant été exposés au DG qui bénéficieraient davantage d'une saine alimentation, considérant leur risque accru d'obésité et de DT2.

En effet, les résultats de cette thèse ont aussi souligné qu'une meilleure qualité alimentaire pendant l'enfance, évaluée à l'aide du score HEI canadien, était associée à une meilleure distribution du tissu adipeux et à une plus faible résistance à l'insuline chez les enfants ayant été exposés au DG *in utero*. Dans cette étude, les enfants exposés ou non-exposés au DG *in utero* avaient un score total de la qualité alimentaire similaire, correspondant à une alimentation requérant certaines améliorations. Cependant, les enfants du groupe contrôle consommaient davantage de fruits et légumes et de fruits entiers que les enfants du groupe exposé au DG, un autre indicateur de la qualité alimentaire fréquemment utilisé dans la littérature. Cela pourrait expliquer le fait que les sous-scores des fruits entiers et des légumes verts foncés et orangés étaient associés à un meilleur profil anthropométrique seulement chez les enfants non-exposés au DG *in utero*. Somme toute, les résultats de cette étude sont en accord avec notre hypothèse initiale et avec la littérature disponible dans la population générale démontrant qu'une alimentation saine serait associée à un meilleur état de santé chez l'enfant.[175] Ils supportent aussi l'idée selon laquelle l'adoption de saines habitudes alimentaires pendant l'enfance pourrait aider à atténuer l'impact du DG sur la santé de l'enfant, comme il a été proposé par certains auteurs.[182, 184] Ainsi, promouvoir la saine alimentation chez ces enfants pourrait représenter une stratégie efficace dans la prévention de l'obésité et du DT2.

Les résultats de cette thèse ont d'ailleurs permis d'identifier certains facteurs individuels et environnementaux associés à la qualité de l'alimentation de l'enfant qui pourraient être intéressants à investiguer dans de plus grandes études d'intervention visant la promotion de saines habitudes de vie chez les enfants ayant été exposés au DG *in utero*. Premièrement, le fait que l'âge des enfants soit négativement associé à la qualité de leur alimentation souligne l'importance d'établir de saines habitudes alimentaires tôt dans la vie de ceux-ci afin qu'ils soient davantage tentés par des choix alimentaires sains lorsqu'ils deviennent plus autonomes dans leur alimentation. En effet, les choix alimentaires des enfants sont principalement guidés par leurs préférences[188], ce qui souligne l'importance d'intervenir tôt dans le développement de leurs préférences alimentaires, tel que mentionné plus haut. D'autres facteurs que les préférences alimentaires sont susceptibles d'influencer leurs choix alimentaires, notamment l'environnement alimentaire à la maison. En effet, plusieurs études ont démontré que les repas pris en famille ont un impact positif sur les habitudes alimentaires des enfants, ces moments étant propices aux discussions entourant la saine alimentation.[194] Les repas pris en famille sont aussi plus souvent cuisinés, donc de meilleure qualité, et les parents présents à table peuvent agir comme modèles positifs pour leur enfants.[210] Les résultats présentés au chapitre 9 ont démontré que les repas pris en famille étaient effectivement associés à la qualité de l'alimentation des enfants du groupe contrôle, mais aucune association n'a été décelée chez les enfants nés de femmes avec DG. L'hypothèse émise pour expliquer ce résultat est que les femmes ayant eu un DG auraient de moins bonnes habitudes alimentaires et graviteraient dans un environnement alimentaire moins sain, ce qui expliquerait que le moment des repas pris en famille ne résulterait pas en une transmission de saines habitudes alimentaires à l'enfant. Les résultats de notre étude supportent d'ailleurs cette hypothèse puisque nous avons aussi démontré que les femmes avec un antécédent de DG consommaient moins de fruits et légumes que les femmes sans DG, et que l'association entre la consommation de fruits et légumes de la mère et celle de son enfant était de plus grande amplitude au sein du groupe contrôle. Ainsi, agir sur l'environnement alimentaire à la maison en sensibilisant les femmes ayant eu un DG à l'importance de consommer des fruits et légumes, autant pour elles que pour leurs enfants, devrait être mis de l'avant dans de futures stratégies de promotion des saines habitudes de vie au sein de cette population.

Finalement, les résultats de mon projet de doctorat ne permettent pas de tirer de conclusion claire quant au rôle de l'allaitement maternel dans la prévention de l'obésité chez les enfants ayant été exposés au DG *in utero*. Selon les résultats présentés au chapitre 5, les enfants ayant été exposés au DG auraient une courbe de croissance différente des enfants non-exposés, avec des valeurs de score Z du poids pour l'âge supérieures à partir de quatre ans principalement, mais cette courbe de croissance ne serait pas influencée différemment par la durée de l'allaitement maternel total ou exclusif entre nos deux groupes. Ces résultats sont en accord avec plusieurs études incluses dans la revue systématique portant sur ce sujet et présentée au chapitre 4 qui ne démontraient aucune association entre l'allaitement maternel et les mesures associées à l'obésité chez des enfants ayant été exposés au DG *in utero*.[215-217] Les résultats de cette revue ont d'ailleurs souligné la mixité des résultats des études portant sur le sujet, ainsi que la difficulté de comparer les études entre elles considérant les méthodes différentes utilisées pour définir les variables d'allaitement maternel ou encore les mesures associées au profil anthropométrique des enfants. Cependant, selon plusieurs des études inclues dans cette revue, l'allaitement maternel serait associé à une diminution du risque d'obésité pendant l'enfance ou l'adolescence dans cette population à risque élevé, alors que les résultats des études réalisées en bas âge (<2 ans) seraient assez contradictoires. Cela pourrait donc expliquer pourquoi nous n'avons pas observé d'association entre la durée d'allaitement maternel et le profil anthropométrique des enfants inclus dans l'étude GDM2 puisque ceux-ci étaient plutôt jeunes, et nos analyses ciblaient la croissance de 0 à 5 ans.

Les résultats la revue systématique présentée au chapitre 4 ont aussi démontré qu'il existe peu d'études portant sur l'association entre la composition du lait maternel et la croissance des enfants ayant été exposés au DG *in utero* (n=2), d'où l'originalité de nos résultats présentés au chapitre 6. Les résultats de notre étude sur le sujet ont permis de constater que le contenu en TG du lait maternel, le principal constituant lipidique du lait, serait corrélé positivement aux valeurs pondérales mesurées à deux mois chez les enfants du groupe contrôle, alors qu'il ne serait pas associé à la croissance des enfants ayant été exposés au DG *in utero*. De plus, les femmes ayant eu un DG avaient un contenu en TG dans leur lait maternel supérieur aux femmes du groupe contrôle, potentiellement expliqué par l'âge plus avancé de ces femmes, l'âge avancé étant un facteur de risque du DG.[49] Nous avons aussi observé une association entre le profil glycémique et insulinémique des femmes et la composition de leur lait, notamment avec les niveaux de TG, de protéines et d'énergie. Ainsi, ces résultats suggèrent que le statut de DG de la femme et son état de santé pourraient influencer la composition de son lait, principalement en lipides, ce qui pourrait potentiellement moduler la croissance des enfants nés de femmes avec un DG. Ces résultats sont intéressants et devront être répétés dans de plus grandes études pour pouvoir tirer des conclusions puisqu'à notre connaissance, aucune autre étude sur le sujet n'a été réalisée dans cette population spécifique.

Forces et limites

Ce projet de doctorat présente plusieurs forces indéniables qui en font son originalité. Premièrement, il cible différentes phases importantes du développement de l'enfant où l'alimentation joue un rôle crucial, soit la période de l'allaitement maternel, l'introduction des aliments complémentaires ainsi que l'alimentation pendant l'enfance. Ce portrait global nous permet donc d'apprécier différents aspects de l'alimentation en bas âge et leur association potentielle avec la santé des enfants à risque élevé d'obésité et de DT2. Les résultats présentés aux chapitres 5, 7, 8 et 9 de cette thèse proviennent de l'étude GDM2, une cohorte composée d'enfants ayant été exposés au DG *in utero* uniquement, excluant les enfants exposés au DT1 ou DT2. Ceci représente une force puisque beaucoup d'études portant sur l'impact du DG sur la santé de l'enfant incluent différents types de diabète, alors qu'ils ont des étiologies différentes et sont traités différemment lors de la grossesse.[122] En effet, les femmes ayant un diabète préexistant à la grossesse sont généralement suivies dès le début de la grossesse, et même avant, alors que le DG est diagnostiqué entre la 24^e^ et 28^e^ semaine de grossesse, ce qui confère un environnement intra-utérin différent selon le moment de prise en charge effectué.[122] De plus, les habitudes de vie de ces femmes peuvent différer, y compris la pratique de l'allaitement maternel de même que leur profil anthropométrique, d'où l'importance de les considérer comme une population distincte.[123] Une autre force de cette étude est la richesse des données qui y ont été recueillies en suivant des méthodes validées. Notamment, l'alimentation des enfants a été mesurée à l'aide de deux rappels alimentaires de 24h, le profil anthropométrique a été mesuré par absorptiométrie à rayon X et le profil glycémique par une prise de sang à jeun. Finalement, une autre force de ce projet de doctorat est l'inclusion de l'étude de la composition du lait maternel des femmes ayant eu un DG afin d'identifier des mécanismes permettant potentiellement d'expliquer l'association entre l'allaitement maternel et la croissance de ces enfants, ce qui a été très peu fait dans la littérature actuelle. De plus, une force de cette dernière étude plus précisément était d'avoir inclus la mesure de la composition corporelle et du profil glycémique des femmes au moment de la collecte de lait maternel, ce qui a permis d'évaluer l'association entre l'état de santé de la femme et la composition de son lait. Cela a permis une meilleure compréhension de l'association entre le DG et la composition du lait maternel. En somme, ce projet de doctorat est original et répondait à un besoin de la littérature actuelle.

Malgré toutes ces forces, ce projet comporte aussi ses limites. Tout d'abord, les résultats présentés proviennent d'analyses secondaires au projet GDM2 et au projet DÉPART, bien que l'ajout du groupe contrôle au projet DÉPART ait été prévu spécifiquement pour l'étude de l'analyse de la composition du lait maternel. Ainsi, la taille d'échantillon des participants inclus dans ces projets n'a pas été calculée en fonction des objectifs réalisés dans le cadre de cette thèse, ce qui a pu limiter la puissance statistique de nos analyses, principalement au sein du groupe contrôle dans le projet GDM2 qui était de plus petite taille. Également, le devis transversal du projet GDM2 n'a pas permis l'étude de l'alimentation de la petite enfance à l'enfance de façon continue, nos analyses étant basées sur des données rétrospectives de l'allaitement maternel et du moment d'introduction des jus. Il serait donc intéressant de répéter ces analyses dans le cadre d'études prospectives, ou dans des projets d'intervention, afin de mieux comprendre le rôle de ces périodes alimentaires sur le développement de ces enfants. Cela pourrait limiter l'erreur de mesure possible associée à la collecte de données rétrospectives. Étudier l'alimentation du nourrisson en temps réel aurait permis de quantifier les aliments ou le volume de lait maternel consommés par les enfants, ce qui aurait permis de tirer des conclusions plus exemptes de facteurs confondants potentiels. L'inclusion des pères et de l'environnement alimentaire à l'extérieur de la maison, comme à l'école ou à la garderie, aurait aussi été intéressant dans cette étude afin de mieux cerner les facteurs pouvant influencer l'association entre l'alimentation et la santé de l'enfant, et afin de mieux évaluer les déterminants de la saine alimentation chez l'enfant. Nous sommes aussi conscients que d'autres facteurs que l'alimentation peuvent influencer l'état de santé d'un enfant, notamment sa pratique d'activité physique, ce qui n'a pas été inclus dans le cadre de ce projet de doctorat.[218] Finalement, les participants de nos projets provenaient majoritairement de familles avec un statut socioéconomique élevé, et étaient principalement caucasiens, ce qui limite la généralisation des résultats obtenus à d'autres populations. Nos résultats sont donc à interpréter avec précaution et ne permettent d'établir aucun lien de cause à effet. Cependant, ils contribuent grandement à l'avancement des connaissances portant sur la prévention des complications en période postnatale chez les enfants ayant été exposés au DG *in utero* et ils ont permis de cibler des éléments pertinents à étudier dans de plus grandes études.

Perspectives

Les résultats de ce projet de doctorat soulignent l'importance d'établir de saines habitudes alimentaires chez les enfants ayant été exposés au DG *in utero* et ce, dès le plus jeune âge. Ils sont en accord avec les recommandations de la Société américaine de pédiatrie qui revendique que les politiques de santé publiques mettent de l'avant l'importance d'assurer une nutrition adéquate dans les 1000 premiers jours de vie de l'enfant.[219]

Bien que quelques études d'intervention visant la modification des habitudes de vie en période postpartum chez des femmes ayant eu un DG aient été réalisées et que certaines d'entre elles incluaient la pratique de l'allaitement maternel dans les habitudes de vie à renforcer, ces études sont généralement basées sur la prévention du risque de DT2 chez la femme.[220] Il serait donc pertinent de développer des interventions qui incluraient l'amélioration des habitudes alimentaires de l'enfant en bas âge dans le but de prévenir son risque d'obésité et de DT2. Les interventions pourraient miser sur l'amélioration de la qualité alimentaire des parents ainsi que la prise de repas en famille afin de vérifier si ces déterminants de la qualité alimentaire, une fois renforcés, influencent positivement la qualité de l'alimentation des enfants, tel que suggéré par nos résultats obtenus au sein du groupe contrôle. D'ailleurs, bien que les résultats de cette thèse puissent suggérer que la mère joue un rôle important sur la santé de son enfant, le rôle du père n'est pas à négliger dans ce processus et devrait être inclus dans de futures études. À la suite de ces études d'intervention, des programmes nationaux ou provinciaux de santé publique pourraient être développés.

Il existe actuellement différents programmes visant le développement sain des enfants, comme la fondation OLO au Québec. Cette fondation offre des aliments sains et des multivitamines prénatales aux femmes enceintes en contexte de vulnérabilité sociale afin d'assurer la croissance optimale de leur bébé, en plus d'offrir des outils et services aux parents pour les aider à acquérir des saines habitudes alimentaires pour eux et leurs enfants.[221] Ce programme a comme objectif ultime d'offrir un meilleur départ dans la vie à des enfants vulnérables. Ainsi, considérant le risque accru d'obésité et de DT2 chez les enfants ayant été exposés au DG *in utero*, et considérant que cette population consomme moins de fruits et légumes que la population générale, il serait pertinent d'établir un programme dans le réseau de la santé qui soit spécifique à cette population à risque afin de renforcer l'adoption de saines habitudes de vie auprès de ceux-ci. Ce projet de doctorat a d'ailleurs ciblé différents éléments qui seraient intéressants à considérer dans un tel programme, comme de l'éducation quant au moment d'introduction des aliments, plus spécifiquement des jus de fruits, ou encore sur l'environnement alimentaire à la maison. D'ailleurs, les femmes enceintes et les nouveaux parents sont généralement à la recherche de conseils pour assurer le bien-être de leur enfant, ce qui fait des périodes de la grossesse et de la petite enfance des moments clés pour intervenir à l'établissement de saines habitudes alimentaires auprès de ceux-ci.[222] De tels programmes ne devraient en aucun cas culpabiliser la femme quant à son rôle sur la santé de son enfant et devraient plutôt miser sur le plaisir de manger sainement en famille et devraient inclure le père ou le partenaire de vie.

Bien que cette thèse ait présenté des résultats peu concluants quant au rôle de l'allaitement maternel sur la prévention de l'obésité chez l'enfant dans les 5 premières années de vie, la littérature scientifique actuelle supporte le fait que la pratique de l'allaitement maternel puisse aider à prévenir cette complication de santé chez les enfants ayant été exposés au DG. De plus l'allaitement maternel procure différents effets bénéfiques sur la santé de la femme et de l'enfant, outre la prévention de l'obésité, d'où l'importance de promouvoir cette pratique auprès de ce groupe de femmes.[223] Considérant que les femmes ayant eu un DG allaitent moins de façon exclusive et moins longtemps, il pourrait aussi être intéressant d'inclure quelques lignes directrices spécifiques aux femmes ayant eu un DG dans les recommandations de l'IHAB afin de renforcer le soutien à l'allaitement auprès de ces femmes et de les informer des effets bénéfiques de l'allaitement pour elle et leur enfant.

Finalement, les résultats présentés dans cette thèse soutiennent l'importance d'agir en période postnatale afin de prévenir les complications associées à une exposition intra-utérine au DG. Prévenir l'obésité chez la descendance féminine des femmes ayant eu un DG aiderait d'ailleurs à briser le cercle intergénérationnel de l'obésité et du diabète.[224] En effet, l'obésité étant un facteur de risque du DG, les femmes ayant été exposées au DG *in utero* et ayant développé de l'obésité sont elles-mêmes plus à risque de développer un DG et de donner naissance à des enfants prédisposés à l'obésité et au diabète.[224] Ainsi, élaborer un programme visant la prévention de l'obésité et du DT2 par l'adoption d'une saine alimentation chez les enfants ayant été exposés au DG *in utero* représenterait un investissement très pertinent pour l'état québécois puisqu'il aiderait à réduire le fardeau financier causé par ces problématiques de santé en croissance continue dans notre société.[225, 226] Il permettrait aussi d'offrir une meilleure qualité de vie à plus long terme à tous ces individus touchés par le DG.

Conclusion générale

En conclusion, les résultats de cette thèse de doctorat suggèrent que les complications associées à une exposition intra-utérine au DG pourraient être atténuées par l'adoption de saines habitudes alimentaires dès la petite enfance. Retarder l'introduction des jus de fruits chez le jeune enfant pourrait être une stratégie efficace pour prévenir la consommation de boissons au goût sucré pendant l'enfance chez ces enfants, contribuant ainsi au développement d'une saine alimentation chez ce dernier. Cela est d'autant plus important considérant que nos résultats suggèrent qu'une saine alimentation pendant l'enfance serait associée à une meilleure distribution du tissu adipeux et une moins grande résistance à l'insuline chez ces enfants à risque. Ainsi, la promotion des saines habitudes alimentaires en période postnatale chez les femmes ayant eu un DG et les membres de leur famille devrait être faite afin de les sensibiliser au rôle de l'alimentation dans l'établissement de leur santé à plus long terme. Ensuite, bien que nos résultats n'aient pas montré d'effet de l'allaitement maternel sur la croissance des enfants de moins de 5 ans, les résultats de la revue systématique présentée dans cette thèse suggèrent que l'allaitement maternel devrait être encouragé chez les femmes ayant eu un DG afin de réduire le risque de surplus de poids et d'obésité pendant l'enfance ou l'adolescence. De la sensibilisation quant à l'influence de l'état de santé de la femme, comprenant son contrôle glycémique, sur la composition de son lait maternel pourrait être réalisée afin de s'assurer que l'enfant allaité bénéficie pleinement de cette pratique alimentaire. Bien que plus d'études d'envergure soient nécessaires pour confirmer nos résultats, cette thèse de doctorat supporte donc l'importance d'une saine alimentation en période postnatale dans l'établissement d'un meilleur état de santé chez les enfants ayant été exposés au DG *in utero*.

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