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Obesity and Immune Status in Children

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Abstract

Purpose of Review—Childhood obesity, with persistent chronic inflammation, is a worldwide epidemic. Obesity causes dysregulation throughout the immune system, affecting the balance and levels of cytokines, adipokines and innate and adaptive immune cells. This review focuses on the impact of obesity on immune function in children: altering the baseline activation state of immune cells and affecting the ability of the host to combat pathogens and malignancy and respond appropriately to vaccination.

Recent Findings—Obesity causes dysregulation of the immune system. Single cell RNA-sequencing of adipose tissue and resident immune cells is quantifying the impact of obesity on the frequency of immune cell subsets and their states. The system-wide alterations in immune function in obesity are most evident upon perturbation, including the response to infection (e.g. increased risk of severe COVID-19 in the ongoing pandemic), vaccination and malignancy. However, mechanistic research in pediatric obesity is limited and this impacts our ability to care for these children.

Summary—We must better understand baseline and perturbed immune health in obese children to determine how to account for altered frequency and function of humoral and cellular immune components in acute infection, during vaccine design and when considering therapeutic options for this complex, medically vulnerable group.

Keywords

Obesity; immune health; immune dysregulation; human immunology

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Introduction

We are experiencing a worldwide pediatric obesity epidemic, stretching from birth through adolescence and continuing through adulthood[1,2]. In the United States, there have been significant increases in childhood obesity over the last 40 years, with more than 13 million obese children and adolescents and with continued increases in the last decade in certain age groups[3]. Black and Hispanic children have increased prevalence of obesity compared to white and Asian American children[3,4]. Worldwide, more than 40 million children under five years of age were overweight or obese in 2016[1] and the continued increase in prevalence of childhood obesity continues, especially in resource limited settings [2]. Obese children experience early onset of obesity related comorbidities[5], the majority will go on to become obese adults (most likely in the most severely obese[6]), and they will experience early mortality[7]. It is not clear how obesity leads to these outcomes and here we will focus on immune dysregulation in the setting of obesity.

Immune health and the effect of childhood obesity

How can we define what is altered or dysfunctional in childhood obesity? We must first measure immune health, which is a challenge. While most organ systems have evidence-based monitoring tests and strategies to assess function (e.g. the EKG or echocardiogram in cardiology and the EEG in neurology), the immune system remains stubbornly challenging to encompass with a single or set of functional tests. The most basic immune evaluation of cellular and humoral immune function includes a complete blood count (CBC) and immunoglobulin levels and vaccine titers, but unless there are deficiencies in cells or antibody levels, this has limited utility. In clinical immunology we frequently enumerate rare immune cell subsets via flow cytometry and test immune cell function, but this has not yielded metrics for the healthy child or adult that synthesizes their “immune health”, simply tables of acceptable levels of each cell type (or function). Without this synthetic understanding, the quantitation of the impact of disease (on that baseline) is complicated.

It is also clear that there is significant variation among “healthy” participants[8] and that variation includes effects of age[9], gender, race and ethnicity and environment on immune cell subset frequency and immune function[9,10]. With regards to environment, early life events affect immune function. Before birth, maternal high fat diet in pregnancy has been linked to increased risk of infant obesity[11], altered infant microbiome[12] and altered cord blood immune components and function including reduced eosinophils and CD4T cells (especially CD4 naïve T cells) altered cytokine[13]. In addition, our diet and microbiome are deeply connected to our immune state. Connections among gut microbiota, serum metabolites and adiposity are the focus of intense research in mice and humans[14,15]. Historically, childhood obesity was linked to alterations in individual metabolites[16], and now across a wide breadth of metabolites [17]. For example, a recent study from our groups showed that gut microbiota produced tryptophan-pathway derivatives, leading to altered miR-181 expression and affecting white adipose tissue (WAT) metabolism in both mice and obese children[18]. This is reviewed in depth elsewhere [19].

Once a population is selected, choosing tissues and cells to measure and compare is also challenging. In mouse studies the routine collection of multiple tissues for deep immunoprofiling is routine, while in human studies we generally study peripheral blood and perhaps one target tissue (if easily accessible). It is important to note that given the challenges in pediatric translational research, there is limited data from healthy (or obese) children to support evidence-based analysis of pediatric immune components and function[20]. In the study of obesity, adipose tissue is frequently studied in adults or mice. There are multiple sources of adipose tissue, including subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). However, these studies are challenging to control in humans as it is challenging to obtain adipose tissue from lean adults or to obtain longitudinal samples of human adipose tissue from the same patient. Studying adipose tissue in children is complex as there are limited programs for pediatric bariatric surgery, which limits both clinical care and research. Recent guidelines from the American Association of Pediatrics argue for increased bariatric surgery access [21].

We have used two strategies to synthesize our current understanding of immune function and dysregulation in childhood obesity. First, when discussing the quantity of immune cells and humoral factors, we have supplemented our knowledge from pediatric human studies with adult human and mouse studies (Table 1). Second, we included the outcomes of clinical perturbations on immune status to deepen our understanding of (limited) multimodal research data; using the response to severe infection, vaccination and malignancy (and immunotherapy), among others, to reveal the degree of dysfunction in childhood obesity (Figure 1).

Immune Health: Quantity of Immune Cell Subsets and Humoral Factors

There are increases in pro-inflammatory cytokines and obese adipose tissue is infiltrated by increased numbers of adipose tissue macrophages (ATM), B cells, T cells and mast cells with decreased numbers of regulatory T cells (Tregs), MAIT cells, ILC2 and invariant NKT cells (iNKT) and accompanied by changes in immune cell frequencies in peripheral blood (Table 1). Of note, throughout our discussions of mouse models of obesity, we will focus on diet induced obesity (DIO) wherein wildtype mice receive a high fat diet (HFD).

Cytokines and Adipokines—In adults, both baseline TNF-α[22] and LPS stimulated TNF-α release are elevated[23], and improve with weight loss[22,23]. In obese children, a similar pattern was seen with elevated IL-6 and TNF-α [24–26].

Leptin is elevated in obesity and it has been shown to directly alter immune function [27,28]. Beyond key roles in hunger, leptin receptors are expressed on T cells and leptin increased IFN-γ secretion and decreased IL-4 secretion[29,30]. Leptin stimulated key cytokine pathways (e.g. JAK-STAT) and enhanced proliferation of PBMCs generally[27], and T cells specifically[29,30]. Leptin has been shown to be increased in obese children[31], correlated with adipose tissue mass and improving with physical training[32] or weight loss[33,34]. In addition to leptin, CRP is elevated and adiponectin is decreased [9,35–37]

Innate Immune Cells—The innate immune system, along with the physical barriers of our skin and mucous membranes, represents our front-line defenses against pathogen

invasion and the site of our interactions with commensal microorganisms. This component of the immune response shows significant alterations in frequency of key cell subsets in adult obesity, including increased VAT mast cells and ATM and decreased VAT innate lymphocyte cells (ILC) type 2, invariant NKT cells (iNKT) and mucosal associated invariant T cells (MAIT). Circulating innate immune cells are complex in their alterations.

Mast Cells, Neutrophils and Eosinophils: In both mice[38] and adult obese humans[39] there is an increased frequency of mast cells in adipose tissue. There are decreased eosinophils in DIO mouse visceral adipose tissue (VAT) [40], while eosinophils are increased in obese adult human SAT[41]. Neutrophils are increased in childhood obesity, ANC and waist circumference more correlated in girls than in boys[9].

Type 2 Innate Lymphoid Cells (ILC2): Obese adults have been shown to have decreased ILC2 in white adipose tissue (WAT)[42]. Depletion of ILC2 in T and B cell deficient (RAG deficient) DIO mice led to increased weight gain, all implying a role for ILC2 in obesity[43].

gdT cells: In obese adult humans there is a decreased frequency of circulating γδT cells and reduced secretion of IFNγ [44]. Mouse models of obesity demonstrate a decreased frequency and reduced function of circulating γδT cells[45], and suggest gdT in AT may provide significant fraction of total IL-17[46].

NKT cells: Levels of circulating NKT cells (CD3+ CD56+) are variable, with some studies showing decrease in adult obesity[47], with others showing no change[48,49]. Circulating invariant NKT (iNKT), identified by their canonical invariant TCR and activated by glycolipid antigens presented by CD1d, are capable of quickly secreting cytokines characteristic of both type 1 and type 2 CD4 T helper responses. Circulating iNKT are also decreased in adult obesity[50,51], but improved in frequency after bariatric surgery and with subsequent weight loss[50]. iNKT are enriched in lean human adult adipose tissue but reduced in frequency in obese adipose tissue[52]. In mouse DIO, NKT cells are reduced in frequency in WAT[40] and depletion of iNKT cells leads to increased weight gain and increased IL-6 and TNF-a. Increasing the frequency of iNKT cells protects DIO mice from gaining weight[50], and activation of iNKT with alpha-galactosylceramide leads to weight loss in DIO mice[50].

In a study of obese children there is no statistical difference in circulating NKT counts at baseline or after a lifestyle intervention [53].

MAIT cells: Circulating MAIT cells are generally decreased in obese human adults[51,54,55] (though not significant different in one study[49]), and they increase after bariatric surgery[51]. In adult obesity, there is a reduced frequency of VAT MAIT cells and obesity increases the relative likelihood of MAIT cells secreting IL-17[51] rather than IFN−γ[54]. The underlying mechanism has been recently clarified; glycolytic metabolism is dysfunctional in obese MAIT cells, in the setting of altered mTORC1 signaling which in turns impairs IFN-γ secretion[55]. There is new evidence in mice that MAIT may increase

pro-inflammatory M1 macrophage differentiation as well as increasing the leakiness of the gut barrier[56].

In one study, childhood human obesity was associated with expanded circulating MAIT cells (rather than decreased as in adults), which were more likely to secrete IL-17 (consistent with adults)[54].

Monocytes: Monocytes are generally not significantly affected by obesity [48,57,58] though they were elevated in some studies[59,60] and in separate studies classical monocytes (CD14++ CD16-) and non-classical monocytes (CD14+ CD16++) are elevated in the blood of obese children respectively[9,35]. Stepping into the complexity of age and race and ethnicity on immune cell frequency, in participants over 12, hemoglobin A1c (an integrated measure of hyperglycemia) had a negative association with intermediate monocytes (CD14+ + CD16+) and a positive association with elevated HDL levels[9]. In addition, race and ethnicity impact inflammatory cell subsets; Black children, who have an increased risk of obesity, lack the correlation of classical monocytes with fasting insulin seen in whites and "other races" (a diverse group in this study including Asian Americans and participants who identify with multiple races) highlighting the need to focusing investigations into mechanisms of immune dysregulation in this understudied (though common) disease and this highly affected population[9].

Adipose Tissue Macrophages: Adipose tissue macrophages (ATM) in mice and adult humans increase in frequency in obesity and are directly responsible for significant secretion of inflammatory cytokines (e.g. TNF-α and IL-6)[61]. Beyond their numbers, there are also effects on the nature of ATM in obesity. Historically, there was a dichotomy drawn between two phenotypes of macrophages: a lower frequency of pro-inflammatory M1 macrophages (e.g. secreting IL-6 and TNF-a) and a marked increase in anti-inflammatory (or 'alternatively activated') M2 macrophages[62], reliant in part on PPARγ signaling, in lean VAT[62]. While the source of IL-4 and IL-13 for the initiation of PPARγ signaling was initially attributed to Th2 cells, there is now evidence that eosinophils and iNKT may play a key role. Where eosinophils are reduced in VAT, this dysregulation of PPARγ signaling may impact macrophages[63]. More recently, there have been studies in mice demonstrating more nuanced strategies for dividing ATMs, one using three groups in mice: Ly6C+, CD9+ and CD9- Ly6C-[64], with evidence of both CD9+ and CD9- ATMs in human adipose tissue as well, with CD9+ ATMs increased in frequency in obese human VAT[64] and a key role for TREM2[65].

NK cells: NK cells bridge the innate and adaptive immune systems and can directly lyse infected and malignant cells. In adult obesity there is variability in peripheral NK cells with evidence of decreased [59,66,67] or increased[60] levels, and studies without statistically significant alterations[47,48,57]). In obese mice and humans there is also variable evidence of NK cell metabolic dysregulation and cytotoxic dysfunction[47,66]. It is important to note that some studies use different markers to define NK cells (CD56+ alone or CD56+ CD16+) and that the impact of obesity on NK cell subsets and function in blood and AT has also been deeply interrogated with variability in outcome[47,48,60,68]. This field is reviewed in

detail in a recent paper[69]. NK cells have been shown to play a role in regulating Adipose Tissue Macrophages (ATM), including increasing insulin resistance [70].

In children, peripheral NK cells (CD56+ CD3-)[71,72] were decreased, with an reduction in $CD56^{dim}$ and increased $CD56^{bright}$ NK cells[71]. NK cells had increased levels of CD69 (an activation marker) at baseline and higher PD-1 after cytokine stimulation. PD-1 at later timepoints in an infection or malignancy is associated with exhaustion in T cells and with impaired NK function[73]. Functionally, NK cells from obese children had impaired proliferation and effector function, and metabolic derangement with increased rates of glycolysis[71].

Adaptive Immune Cells—Synergistic with pattern-based innate immune responses, T and B cells are antigen-specific lymphocytes which are fundamental to immune function, providing for the nature of the immune response (CD4 T cells) and direct cytotoxicity (primarily CD8 T cells) as well as antibody production (B cells), which are all affected by obesity (Table 1). VAT demonstrates increased infiltration by B cells and CD4 and CD8 T cells in obesity, and circulating cells are more complex in their alterations, with an intriguing finding that obesity yields increased expression of inhibitory receptors (e.g. PD-1) at baseline.

B cells: B cells play important roles in both humoral immunity, by generating antibodies, as well as serving as antigen presenting cells and thus contributing to T cell activation. Circulating B cell levels are variable in obese adults, with studies demonstrating stable levels[48,57,60] or elevated levels[59]. There may be increased infiltration by B cells of SAT in obese humans[60]. In DIO mice, B cells have been noted to infiltrate obese VAT in greater frequency than lean VAT where they contribute to the development of insulin resistance (IR). Depletion of B cells leads to improved metabolic state in DIO mice and, conversely, transferring IgG from a DIO mouse yields IR in recipients [74].

In obese children there was no difference in overall peripheral B cell frequency[72] and no significant increase in peripheral memory B cells, but increased naïve B cells (CD10- CD27-) and immature transitional B cells (CD10+ CD27+) [53].

CD3T cells: Obese adults show a wide range of peripheral total CD3T cells versus non-obese controls, from elevated[59], to not significantly different[57] and less frequent [23,48]. Obese children did not show significant change in peripheral CD3T cell counts versus lean children[72].

Peripheral CD4 T cells were generally stable in obese adults versus non-obese adults[48,51,52,58,60], though increased levels have also been seen[59]. Some studies showed a decrease in memory CD4T cells[23], one showed an increase in CD4T effector memory (TEM) [75,76], another with increased naïve T cell (TN), central memory T cell (TCM) and effector memory re-expressing CD45RA (TEMRA) subsets[77]. Obese children showed no significant change in total peripheral CD4 T cell frequency[72].

Peripheral CD8 T cells were generally stable in obese adults versus non-obese adults[48,51,52,57,58,60], though decreased [23] and increased [59] levels have also been seen. Obese children showed no significant change in peripheral CD8 T cell frequency[72].

In obese adults, SAT contained more CD4 and CD8 T cells[78].

In DIO mice, there was decreased level of naïve CD3T cells in subcutaneous adipose tissue with increase in effector memory T cells (Tem) in visceral adipose tissue (VAT) [78] with reduced TCR-Vβ diversity[78–80] . VAT is a niche for memory T cells which provide antigen specific protection to infection when transferred to naïve mice[81]. There is evidence in DIO mice that effector CD8T cells [28] infiltrate the VAT before macrophages[82] and that depletion of CD8 T cells reduced M1 macrophages and inflammatory cytokines[82]. In addition, STAT3 is elevated in DIO mice VAT T cells, with significant reductions in amount of AT in *Stat3*$^{-/-}$ mice and increased VAT CD4 TN and Th2 cells and reduction in Th17 and Th1, with improved frequency of M2 macrophages, partially correcting DIO immune dysregulation [83].

Altered balance of CD4 T cell subsets: CD4T cell subsets include those involved in tolerance (regulatory T cells, Tregs), helping B cells (T follicular helper cells, Tfh), combating helminths and contributing to allergy (T helper type 2, Th2), combating viral and intracellular pathogens (T helper type 1, Th1) and combating extracellular pathogens and contributing to autoimmunity (T helper type 17, Th17).

Regulatory T cells (Tregs) are variable in human adult obese blood including increased[77] and decreased levels[76], as well as settings with no detectable change[51,60]. In obese children, peripheral Treg levels were not significantly changed[53]. Tregs are decreased in obese adult VAT[84,85].

The balance between Th1 v. Th2, between anti-viral and anti-helminth/allergic immune tone, has been studied in adults and children. There is some evidence that CD4 T helper type 2 (Th2) were increased in adult obese peripheral blood[77], though they are not significantly altered in obese children[72]. Th1 cells were not significantly altered in obese adults, but were increased in obese children in one study (based on IFNg+)[72] and not significantly altered in another (based on CXCR3+ CD45RO+)[53]. In separate studies there no significant increase in frequency of Th1 between obese and non-obese children who are non-asthmatic [86,87]. In a study of VAT and SAT in adult obesity, there was significant Th1 and Th2 infiltration (but no comparison to healthy or post-surgical AT), simply enriched Th1 and Th17 in VAT v. SAT[88]. Of note, Th1 cells correlated with CRP and IL-6 and Th2 were inversely correlated CRP[88].

In obese adults increased[89] or not significantly altered circulating Th17[77] have been found. In childhood obesity, circulating Th17 cells were increased [90,91]. VAT from adult obese patients with insulin resistance VAT was enriched for Th17 and Th22 cells[92]. A mouse DIO study demonstrated that IL-17, which can also be secreted by γδ T cells, is an inhibitory factor in obesity[46].

Tfh directly assist B cells in activation and one study of pre/post bariatric surgery obese adults demonstrated more IL-10 and less pro-inflammatory cytokines from circulating Tfh post-bariatric surgery[93].

Altered states of CD8 T cells: In the presence of chronic antigen exposure **and** inflammation (e.g. malignancy and chronic infection) an immune process known as exhaustion takes place, which leads to upregulation of inhibitory receptors (IR), altered transcription and epigenetic state and poor function of the affected cells[94]. In DIO mice, non-human primate obesity and obese adults there is increased expression of PD-1 on CD8 T cells (a key IR in exhaustion) and evidence of reduced effector function in each species[95]. It remains unclear if there is truly exhaustion, and much work remains to be done. In addition, while the presence of inflammation is clear, it remains unclear what the antigenic stimulus is (or whether other pathways are active that remove this need).

Beyond altered circulating T cell subset and functional alterations, in DIO VAT the frequency of senescent T cells (CD153+ PD-1+ CD44hi CD4T, able to secrete osteopontin) is increased and those cells demonstrated poor IL-2 and IFN-γ secretion[96]. A recent strategy targeted those cells for depletion in DIO mice using a CD153 vaccine and improved insulin tolerance[97].

Immune Health: Quality of Immune function

Beyond enumerating altered immune components, there is clear evidence of the broad impact of obesity on the core mechanisms of immune function and here we will focus on evidence of impaired function in obesity and how this impacts the health of obese children (Figure 1).

Response to Vaccination—The effect of obesity on vaccine response is mixed as there are only a handful of studies which are generally small and focused on adult patients with minimal evidence in children. In adults, responses to Hepatitis B vaccine have been shown to be reduced in obesity[98–102]. There has been conflicting evidence of efficacy of influenza vaccine response, with higher initial influenza IgG antibody titers, followed by a more pronounced decline over 12 months[103] and another study without impact of obesity [104]. In addition, there was decreased CD8+ T cell activation with influenza vaccination and subsequent restimulation with influenza protein[103] and increased risk of influenza infection in vaccinated obese adults[105]. Most recently, obese adult recipients of the 23-valent pneumococcal vaccine demonstrated improved responses[106].

Decreased response to Hepatitis B vaccine has also been seen in adolescents[107]. Tetanus titers have been shown to be reduced in overweight adolescents compared to healthy weight children[108]. In children, there was no effect of BMI on influenza vaccine response after two doses (though there was not a 12 month assessment)[109]. While obese children who had received influenza infection missed more days of school, the influenza vaccine protected obese children from becoming infected with influenza given consistent frequency of influenza in vaccinated obese and non-obese children (of note, rates of influenza infection were also consistent between obese and non-obese *unvaccinated* children)[110].

Overall, the impact of obesity on vaccine response is unclear, especially in children, and requires further study.

Response to acute infection, including both the COVID-19 and H1N1 pandemics—The data in pediatric ICU outcomes is somewhat mixed, with some data showing increased mortality in PICU admissions [111], and some not[112]. In adults, NHANES data was assessed from 1971–2000 and found no evidence of excess deaths in obesity in the context of infections[113]. However, there is evidence in obese adults and children[114] of increased surgical site infections and evidence of increased morbidity from lower respiratory tract infections[115].

In obese adults there is clearly increased morbidity and mortality for certain respiratory infections including H1N1 influenza[116,117] and the current COVID-19 pandemic[2,118,119]. The mechanism for this increase is unclear, and an active area of study. Given how rare the cases of severely affected children and young adults are, there is active international collaboration to study whether there are novel or yet undiagnosed inborn errors of immunity in severely affected children and young adults with COVID-19[120]. Childhood obesity also may increase the risk of severe COVID-19[121]. Interestingly, we have learned from primary immune deficient patients who lack B cells (and have survived COVID-19) that B cells may be expendable[122], and the T cell immune dysregulation discussed above (e.g. increased PD-1 levels on CD8 T cells, altered CD4 T helper subsets, altered cytokines and adipokines, etc) may increase the risk of severe infection with viral infection.

Exhaustion in obesity with improved response to immune checkpoint inhibition

Childhood obesity increases the risk of cancer in early adulthood[123,124], much like the increased risk of malignancy in obese adults[125]. However, there is recent evidence of altered response to novel oncologic therapy in obesity [126]. This type of therapy, used for some forms of malignancy, is known as immune checkpoint inhibition and uses monoclonal antibodies to target elevated inhibitory receptors (e.g. PD-1) to reinvigorate stalled anti-tumor CD8 T cell immunity[94]. In obese adults there is evidence of both increased expression of PD-1 (a key inhibitory receptor and a target of immune checkpoint inhibition) on CD8 T cells in the tumor microenvironment (TME) and better outcomes with checkpoint inhibitor therapy (monoclonal antibodies directed towards inhibitory receptors) [95,127]. There is not yet published evidence on PD-1 in obese children and checkpoint inhibition in pediatric oncology has been less effective than in adult cancer[128–130] to this point, so there is no current evidence as to the impact of pediatric obesity on checkpoint inhibition response.

Effect of weight loss on immune function

Supporting the evidence of obesity in altering immune function, there is evidence across multiple studies of adult humans that weight reduction can improve immune function, as well as evidence of overall improvement in mortality. CD3T cells (specifically CD4 T

cells and the CD4+ CD45RO+ memory T cell subset) were decreased in obese adults as was the T cell proliferative response to PHA [23], post-diet induced weight loss there was improvement in T and NK cell counts and response of T cells to PHA and concanavalin A[23]. In the same study, prior to weight loss, both baseline TNF-α and LPS stimulated TNF-α release were elevated[23], and the latter improved with weight loss. In obese adults there was improved cytokine production by T cells [131], as well as from bulk PBMCs stimulated with PHA (phytohemagglutinin)[132] after bariatric surgery. PBMC cytotoxicity was decreased in some studies of obese adults[132], with improvement in effector mechanisms after bariatric surgery [132]. Finally, in obese adolescents there was elevated IL-6 and leptin that improved with bariatric surgery, along with a resulting increase in adiponectin[133], with a similar reduction in leptin in adults post-surgically [132].

Conclusion

Childhood obesity is one of the most common non-communicable inflammatory diseases worldwide. However, while extremely common and with significant effects on the balance of the components of the immune response and concern for significant impact on immune function (given the alterations in response to some pathogens, concern for impact on vaccination responses and evidence of immune dysregulation), this is an understudied disease. More work must be done both to understand immune health at baseline in pediatrics, the alterations imposed by pediatric obesity, as well as response to perturbations (including infection, vaccination and weight loss, specifically bariatric surgery) to better care for this medically complex and fragile population.

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Abbreviations:

ATM	Adipose Tissue Macrophages
DIO	Diet induced obesity
HFD	high-fat diet
ILC2	Innate lymphoid cells, type 2
NK	Natural Killer cells
iNKT	invariant NK T cells
MAIT	mucosal associated invariant T cells
SAT	subcutaneous adipose tissue

scRNA-seq	single cell RNA sequencing
TCM	central memory T cells
TEM	effector memory T cells
TEMRA	effector memory T cells re-expressing CD45RA
Texh	T cell exhaustion
TMEM	memory T cells
TN	naïve T cells
TLR	Toll-like receptor
Th2	type 2 CD4 T helper cells
Th17	type 17 CD4 T helper cells
VAT	visceral adipose tissue

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ethnicity, uncovering discordant connections in different groups that highlight the need for more study of diverse participants in both heathy and obese cohorts. (**)

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Key points

- There are significant alterations in childhood and adult obesity in both the quantity and activation state of both peripheral and target tissue immune cells
- Obese children and adults experience increased morbidity with some types of pathogens, including COVID-19, consistent with the concern for immune dysfunction based on altered immune cell components and function
- There is a dearth of investigation into pediatric immune health generally and the impact of childhood obesity on immune function specifically

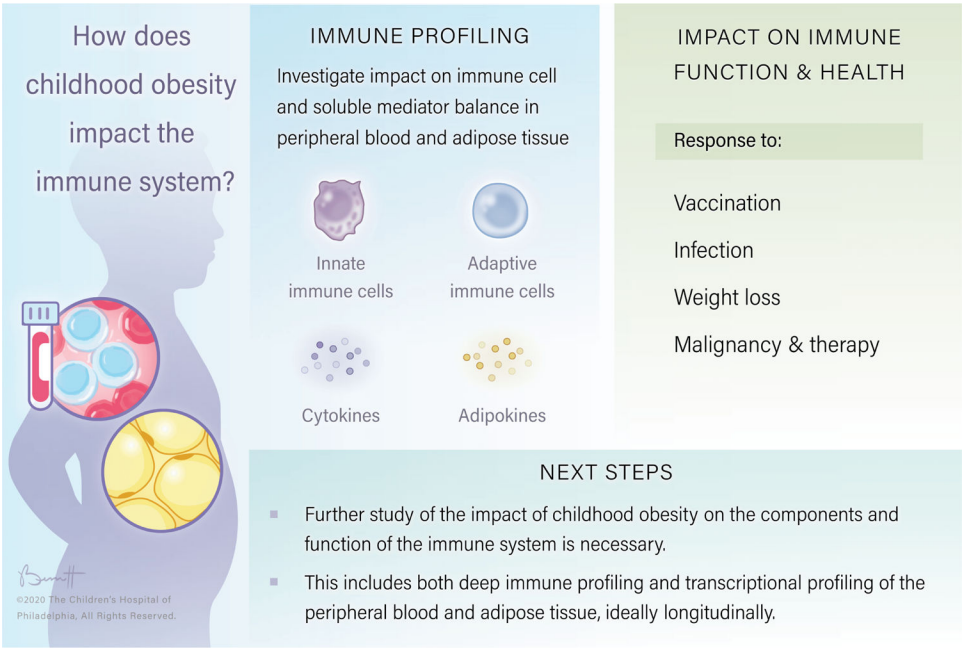

Figure 1: Impact of childhood obesity on immune function.

In order to measure the impact of childhood obesity on immune function it is necessary to start by quantifying levels of cytokines and adipokines as well as key immune cell subsets. To measure impacts on function we examine the effects of obesity on response to vaccination, acute infection, malignancy and oncologic therapy as well as weight loss. "©2020, The Children's Hospital of Philadelphia, All Rights Reserved"

Table 1:
Impact of obesity on key human immune cell subsets.

Within AT, alterations are in VAT if not listed as SAT. Up arrows indicate enriched populations, down arrows indicate less prevalent populations and sideways arrow indicates no significant difference measured. AT = adipose tissue, PB = peripheral blood.

Cell type	Adult		Child	
	AT	PB	AT	PB
B cells	→VAT p = 0.055 ↑SAT [60]	→[23,48] ↑[59]		↑Bnaive [53] →Bmemory [53]
Vaccine Responses	n/a	↓Hepatitis B [98–102] →Influenza [103–105] ↑PPSV23 [106]	n/a	↓Hepatitis B [107] ↓Tetanus [108] →Influenza [109,110]
CD4 T cells	↑[78]	↑[59,77] ↓[23] →[48,51,52,58,60]		→[72]
Naïve CD4 T cells		↑[77]↓[57] →[23]		
Non-naïve CD4 T cells		↑[75,76] TEM, ↓[23] TMEM, ↑[77] TN, TCM, TEMRA		
Th1 cells	→[92]	→[77]		→↑[53,72]
Th2 cells	→[92]	↑[77]		→[72]
Th17 cells	↑[92] in insulin resistant ptx			
Th22 cells	↑[92] in insulin resistant ptx			
Tregs	↓ [84]	→[51,60] ↑[77] ↓[75]		→[53]
CD8 T cells	↑[78]	↓[23] ↑[59] →[48]		
Naïve CD8 T cells	→[77]			
Non-naïve CD8 T cells	→[77]			
NK cells	variable[69]	↓[59,67,68] →[47,48,57] ↑[60]		↓[71]
NKT cells	↓[52]	↓[47,50,52] →[48,49]		→[53]
Monocytes	n/a	→[48,57,58] ↑[59]		→[53] ↑[26]
Classical	n/a	↑[60]		↑[9] ↑[26]
Non-classical	n/a	↑[60]		↑[35]
Adipose Tissue Macrophages (ATM)	↑[134]	n/a		
Pro-inflammatory (M1) (v. Anti-inflammatory (M2) ATM	↑[60,62]			
CD9+ ATMs	↑[64,65]			
Eosinophil	↑[41] in SAT			
Neutrophil		↑[59]		↑[26]
Mast cell	↑[38,39]			
MAIT cell	↓[51,54]	↓[51,54] →[49]		↑[54]