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ETIOLOGY OF OBESITY (T GILL, SECTION EDITOR)

Viral Infections and Obesity

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Abstract
Purpose of review Obesity is a multifactorial disease that is now endemic throughout most of the world. Although addressing proximate causes of obesity (excess energy intake and reduced energy expenditure) have been longstanding global health priorities, the problem has continued to worsen at the global level.
Recent findings Numerous microbial agents cause obesity in various experimental models—a phenomena known as infectobesity. Several of the same agents alter metabolic function in human cells and are associated with human obesity or metabolic dysfunction in humans. We address the evidence for a role in the genesis of obesity for viral agents in five broad categories: adenoviridae, herpesviridae, phages, transmissible spongiform encephalopathies (*slow virus*), and other encephalitides and hepatitides. Despite the importance of this topic area, there are many persistent knowledge gaps that need to be resolved.
Summary We discuss factors motivating further research and recommend that future infectobesity investigation should be more comprehensive, leveraged, interventional, and patient-centered.

Keywords Adenovirus · Human · Animal · Adiposity · Infectobesity · Pawnobe · Transmissible Spongiform Encephalopathy

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Introduction

Simplistic explanations for obesity enjoy popular appeal, but obesity is complex and multifactorial [1]. By contrast, the germ theory of disease has faced considerable scrutiny since it was first proposed, spurring over a century of rigorous infectious disease inquiry. Likewise, the idea that infectious agents cause obesity has also faced criticism and spurred research. Thus far, numerous infectious agents have been shown to cause experimental lab animals to gain body fat (i.e., infectobesity) and serologic studies have demonstrated humans with obesity are often infected with the same agents (Table 1). For example, substantial epidemiologic evidence links adenovirus (Ad) 36 and obesity with over 10,000 subjects in a recent meta-analysis [20]. Further investigation of infectobesity is needed to understand the relevance of obesogenic infectious agents in human obesity pathophysiology, clinical obesity management, and public health.

We provide a focused overview of viruses as causative agents of obesity including overall biological plausibility of infectobesity, discussion of the theoretical selection benefits for a virus that can alter host metabolism, consideration of adipogenesis as a host adaption to infection, discourse of specific agents and mechanisms, and proposed priorities to resolve persistent knowledge gaps. Five viral agent categories with varying evidence of infectobesity causality are considered: adenoviridae, herpesviridae, phages, transmissible spongiform encephalopathies (*slow virus*), and other encephalitides and hepatitides.

Biological Plausibility

Infectobesity is biologically plausible when considering a pathogen's fitness, (i.e., how well a pathogen survives and

Table 1 Adipogenic virus evidence summary

	Adenoviridae [2•]	Herpesviridae [2•, 3•, 4, 5]	Phages [6–8]	TSEs [9••, 10–16]	Other [3•, 17–19]
Members with any adipogenic evidence	SMAM-1, Ad-5, Ad-9, Ad-31, Ad-36, Ad-37	HSV-1, CMV, HHV8	Gut phages	BSE/CJD variant, kuru, scrapie variants	HCV, RAV7, BDV, CDV
Natural host of above members	SMAM-1: avian Others: humans	HSV-1, CMV, HHV8: Humans	Likely all animals with a gut have gut phages.	BSE: cattle scrapie: sheep kuru: human	HCV: human, RAV7: chickens, BDV: horses, sheep, CDV: dogs
Presence in humans reported	SMAM-1, Ad-5, Ad-31, Ad-9 Ad-36, Ad-37	HSV-1, CMV, HHV8	Yes, ubiquitous.	BSE, CJD, and kuru	HCV, BDV
Livestock reservoir	SMAM-1, Ad-36: chickens	Unknown	Yes, ubiquitous.	BSEs: cattle scrapie: sheep	RAV7: chickens, BDV: horses, sheep
Lipogenic *in vitro*	Ad-5, Ad-9, Ad-31, Ad-36, Ad-37 cause adipocyte differentiation and lipid accumulation	CMV, HSV-1 (HSV-60), and HHV8 cause lipid accumulation	Unknown	Unknown	HCV enhances lipid synthesis, CDV enlarges adipocytes
Adipogenic in animals	Ad-36, Ad-37: chickens, Ad-36, Ad-5: mice, Ad-36: rats, marmosets	Unknown	Gut phages following risperidone treatment: mice	BSE: primates scrapie, CJD variants: mice	BDV, CDV: mice, RAV7: chickens
Human association observed	Ad-5 childhood obesity, Ad-36 childhood, adult obesity and BMI, SMAM-1 BMI	CMV metabolic syndrome components, HSV-1 obesity in some studies	Indirectly—adipogenic gut microbe transfer associated with heavier human donor	Kuru obesity and/or bulimia during early disease in humans	HCV genotype 3 insulin resistance

propagates). For instance, cytomegalovirus (CMV) reprograms glucose and lipid metabolism through multiple mechanisms to enhance biosynthesis of the viral envelope and other substrates for viral progeny [21, 22], and interruption of the cellular effect via cholesterol lowering medication inhibits production of substrates and viral particles [23]. Likewise, Ad-5 enhances host glycolytic enzyme activity that increases nucleotide biosynthesis for progeny [24, 25]. Similarly, gut microbes can metabolize dietary fat into acetate, and acetate causes rodents to eat more fat [26], which theoretically should promote survival of microbes best suited for digesting fat.

Symbiotic host selection is also a theoretical possibility: that is, if an obesogenic host phenotype is selected, then a virus conferring this phenotype could be simultaneously selected. Recent livestock domestication includes aggressive selection for metabolic features like efficient fat gain; when an organism (e.g., heaviest cow) is selected, some of its associated microbiota are also selected [9••]. Although there is uncertainty about how artificial selection of livestock impacted livestock microbiota, the proposition is not entirely theoretical. For instance, there is evidence that numerous infectobesity agents have livestock reservoirs [9••]. By similar logic, purposeful selection of microbes associated with obesity (or other traits) could provide an experimental model for selecting infectobesity agents and has been described elsewhere as "pawnobe" evolution [9••].

A third perspective on biological plausibility is that host immune responses could be adaptive in the short term but promote obesity risk over the long term if adipose tissue has multiple biological functions. Although energy storage is the most visible purpose for adipocytes (i.e., fat cells), the immunologic roles of adipose tissue are also noteworthy. For instance, some have proposed adipocytes as the origin of the adaptive immune system in vertebrates [27]. In fact, there is evidence of plasticity between macrophages and adipocytes bearing similar cellular markers, sharing the same stem cell lineage, and executing similar functions [28]. Macrophages enlarge as they collect and engulf pathogens or cellular debris during phagocytosis, and adipocytes sequester excess glucose and lipophilic toxins and engage in antimicrobial functions. For instance, the presence of a pathogen (*Staphylococcus aureus*) leads to acute expansion of local adipose tissue (increased size and number of adipocytes) and elaboration of an antimicrobial peptide (*cathelicidin*) and experimentally blocking this function made mice more vulnerable to pathogen invasion [29, 30]. Adipocytes also modulate immunologic cell activity (e.g., CD4+ T cells) via fatty acid release [31]. At the same time, the localized benefit of expanded adipose tissue could be outweighed by obesity risk in a chronic infection with ongoing systemic inflammation. Human studies have shown obesity is independently associated with systemic inflammation [32, 33], and the total burden of multiple chronic infections has been associated with body fat among men [34].

Adenoviridae

Adenoviridae is the most widely investigated adipogenic viral family. Systematic reviews and meta-analyses of human epidemiologic data show a robust association between Ad-36 viral antibodies [20, 35, 36] and human obesity. A systematic review of adipogenesis evidence among Ad-5, Ad-9, Ad-31, and Ad-37 has also been published [2•]. The evidence can be divided into laboratory, animal, and epidemiologic categories [37•]. Adipocyte progenitor 3T3-L1 cell infection with Ad-9, Ad-31, Ad-36, and Ad-37 *in vitro* enhances adipogenesis with more lipid content, more numerous adipocytes, and/or more commitment to an adipocyte lineage. Ad-36 is adipogenic in Colo-320 cells [38]. Ad-5 is glycolytic in epithelial cells and adipogenic in Colo-320 cells, but not 3T3-L1 cells [2•, 3•, 24, 38].

Animal experiments have demonstrated Ad-5 and Ad-36 infection cause rodents to gain body fat [39, 40], and Ad-36, Ad-37 (compared to Ad-2), and SMAM-1 infections cause chickens to gain body fat, but not Ad-31 infection [41–43]. Ad-36-infected chickens also transmitted an obesogenic phenotype to cage mates and to blood transfusion recipients [41]. Observational (natural) Ad-36 infection in non-human primates was positively correlated with weight gain in one study that identified time of infection [44] while another small study comparing primates with any prior exposure to Ad-36 showed non-significant differences in body weight, but persistent differences in glycemia [45]. Non-human primate infection with adenovirus caused substantial increases in body fat shortly after infection [44].

Epidemiologically, the association between adenoviridae and obesity in humans is stronger among children with Ad-5 and Ad-36 [2•, 35, 46] while Ad-8 [2•] also had a similar trend toward obesity among children but no association among adults for Ad-5 or Ad-37; however, association between Ad-36 and obesity is also present in adults in meta-analyses conducted by different international groups including a combined analysis of over 10,000 (mostly adult) subjects [20, 35, 36]. Additionally, Ad-31 has a non-statistically significant association of similar magnitude as Ad-36 in adults, and antibody to a non-human adenovirus SMAM-1 was associated with human body mass index in adults [2•, 47].

The mechanisms by which Ad-36 promotes adipogenesis are known. The presence of viral protein early 4 open reading frame 1 (E4-ORF1) is necessary and sufficient for acute adipogenic effects [2•]. The virus activates the so-called master-switch of adipocyte development, peroxisome proliferator-activated receptor-γ (PPARγ), signaling adult stem cells to become adipocytes [48, 49]. Ad-36 causes cells to express glucose transporters (Glut4 & Glut1) by activating the Ras pathway (upregulating phosphatidal inositol 3-kinase) even without insulin signaling [50–52]. Glucose transporters bring glucose into the cell and upregulated fatty acid synthase rapidly converts additional glucose to fatty acids [53], meaning adipocytes are larger and more abundant shortly after infection.

Chronic adipogenic mechanisms are also understood as infected cells show lower fat oxidation [2•, 54] and hormone alterations in insulin and leptin occur [53, 55]. Leptin hormone ordinarily provides negative feedback on appetite after lipid accumulation, but infected adipocytes secrete less leptin [53]. Insulin regulates glucose metabolism and humans with a history of Ad-36 infection have a lower concentration of insulin [55]. Additionally, Ad-36 infection causes systemic inflammation; a knock-out study in mice showed that an inflammatory protein, monocyte chemoattractant protein 1 (MCP-1), is necessary for maintaining Ad-36-induced obesity [56]. Studies using mice with genetic deletions have demonstrated the importance of MCP-1 and PPAR-γ for obesity and insulin resistance in mice without infection [2•, 57], so this is also a plausible mechanism for obesity maintenance in Ad-36 infections. This is supported by a study which showed lowering MCP-1 with anti-inflammatory mulberry extract reduced body fat in Ad-36 infected mice [58].

Herpesviridae

At least two herpesviridae, cytomegalovirus (CMV) and herpes simplex virus 1 (HSV-1), appear to be lipogenic. CMV has been connected with several components of metabolic syndrome, including higher blood pressure after infection [4] and metabolic dysfunction among the general population without obesity [5]. *In vitro*, CMV alters fatty acid synthase and other metabolic enzymes, engorging the host cell with lipid as suggested by the name "cytomegalovirus" [3•, 21, 22]. CMV fitness is influenced by metabolic changes and statin medication reduced the production of progeny [23]. Cross-sectional association between HSV-1 and obesity has been identified in some studies [34, 59, 60], and there are links between total burden of infections, inflammation, and obesity [34, 61, 62]. One study found HSV-1 and CMV were connected to central obesity in women, but not men, suggesting a mechanism of chronic inflammation or other host factors [62]. The genetic polymorphism predisposing individuals to HSV-1 infection is associated with higher body mass, arguing against reverse causation (i.e., genetic susceptibility to herpes necessarily comes before obesity) [59].

In vitro evidence supports an adipogenic role for HSV-1. The HSV60 segment of synthetic HSV-1 DNA enhances proliferation of adipose cells while reducing leptin release [63], similar to AD-36. HSV-1 also alters cellular metabolic processes related to glucose and glycolysis [3•]. It is likely that Kaposi sarcoma herpes virus (HHV8) is also lipogenic [3•] *in vitro*, but an association with human obesity has not been identified.

Phages

Research has shown that the gut microbiome, including bacteria, viruses, and other microscopic organisms, likely have a causal influence on host body weight. A stool transfer from a heavier human twin caused mice to gain weight [6]. The mice (like Ad-36 infected chickens) also transferred a stool-derived metabolic phenotype to cage mates [6]. In human adults, numerous probiotic formulations cause modest weight loss [64, 65] although the quality and size of the studies were limited. Finally, several *Bacillus* spp.-derived probiotics cause commercially favorable weight gain in multiple agricultural animals [66–68].

Potential mechanisms for the microbiome to influence weight are numerous. Whole-genome analysis at the strain level correlated host obesity with *Lactobacillus* genes for oxidative stress and glycolysis [69]. Acetate production from microbiota caused hyperphagia and obesity among rodents through a parasympathetic nervous system pathway [26]. Non-specific inflammatory mechanisms similar with adenoviridae and herpesviridae are also possible. Bacterial translocation could contribute to low-grade inflammation: lipopolysaccharide binding protein (translocation marker) serum concentration was associated with overweight and obesity in a population-based study [70]. Additionally, a probiotic has been shown to prevent the inflammatory infiltration of macrophages into adipose tissue that is a feature of the persistence of Ad-36 obesity in mice [56, 71].

Despite rapidly emerging causal evidence, findings are modest, and meta-analysis of observational data shows there are relatively weak correlations between bacterial taxa and obesity across studies [72]. Phages are more diverse than the bacteria they infect and represent the most numerous biologic group known [73], and so, the stool virome could be important in fat gain and obesity. Phage in human stools is capable of shifting the dynamics of the gut microbial ecosystem *in vivo* [73], and host stress may affect phage composition of gut microbiota [7]. The role of phages in obesity transmission was identified in mice which like humans gain weight after treatment with risperidone, an antipsychotic medicine [8]. Risperidone depresses energy expenditure, inducing weight gain in mice. Stool transplanted from risperidone-treated mice causes transference of both weight gain and depressed energy expenditure. Phage isolated by filtration from among gut microbes was sufficient for lowering energy expenditure and causing weight gain in recipient mice [8].

Transmissible Spongiform Encephalopathies

Numerous transmissible spongiform encephalopathies (TSEs) exist that transmit obesity to at least one host species [9••]. The specific TSE agent is often described as a "prion" or "slow virus." Controversy exists over whether a misfolded protein or its associated 25-nm viral particle is the transmissible agent [74]. Recent evidence using nuclease and keratinase indicates misfolded proteins are not sufficient to transmit TSEs while nucleic acids are sufficient; therefore, including TSEs in our discussion of viruses is appropriate [75, 76]. This class of transmissible agent also shares features with adenoviridae (Table 1—livestock reservoirs, primate experiments, and human observational evidence). The neurodegenerative disorder Kuru is commonly associated with obesity and bulimia in humans in early stages of disease [10]. A Creutzfeld Jakob disease (CJD) agent variant (263 K-sc) with lower virulence causes "extreme obesity" in mice [11], and several scrapie agents cause hyperphagia, fat gain, and/or weight gain in some mouse strains [12–14]. Infection with a high dose of bovine spongiform encephalopathy has a different time course for the metabolic and neurologic manifestations in non-human primates [15, 16]. In a feeding study, the agent initially remained confined in the gut and caused rapid weight gain within 1.5 years that was not seen in controls [15]. The mechanism of weight gain appears related to interaction between the agent and gut endocrine cells [15], but pancreatic involvement has also been observed [16, 77], perhaps related to a type 2 diabetes phenotype, suggesting the possibility of endocrine mechanisms. Further, adrenalectomy prevents mice from gaining weight with another TSE (scrapie) and infection of the hypothalamus augments weight gain, suggesting a hormonal pathway through the hypothalamus-pituitary-adrenal axis [14].

Fatal CJD and kuru are relatively rare in humans, and the possibility of TSE relevance in human obesity at a population level might be dismissed because of the prevalence of human TSEs. However, genetic susceptibility to CJD has shown a modeled penetrance of 0.96 after age 80, which may reflect ubiquitous infection or a form of CJD that is not horizontally transmitted [78]. The prevalence, incidence, and other epidemiologic features of TSE-associated viruses are unknown in humans. Evidence suggests neurologic manifestations are eventually 100% with a very high dose of infectious agent (≥5 g), but infection rates after feeding low dose agent (0.05 and 0.005 g) are less clear, perhaps because of longer incubation [16]. CJD (variant 263 K-sc) causing "extreme obesity" in mice required a 17-times higher dose for GT1 cells to demonstrate prion proteins [11], and the initial stages of primate infection appear confined to the gut [15]. Even if these agents are not relevant for human obesity at a population level, they demonstrate further proof of concept with causal evidence that infectious agents are able to cause rapid weight gain [15] and alter host eating behavior [14].

Other Encephalitides and Hepatitides

Other known examples of viral infectobesity occur in animals with pathogens of the brain or liver [17]. Because these organs have numerous roles in metabolic regulation, identifying human pathogens could be important. Adenoviridae [79, 80] are

also known to infect the liver. Hepatitis C virus (HCV) alters cellular metabolism to upregulate fatty acid synthase and glycolosis similar to some adenoviridae and herpesviridae [3•]. Human studies have shown an association between HCV, insulin resistance, and/or metabolic syndrome possibly related to hepatic steatosis (appearing worse with genotype 3) [18]. Other examples include the following: Borna disease virus (BDV) infects the hypothalamus and causes obesity in mice [17, 81]; Rous associated virus 7 (RAV7) causes obesity, ataxia, and liver steatosis in chickens [17, 82]; and canine distemper virus (CDV) alters brain catecholamine pathways in mice [83] and causes enlarged adipocytes [17].

The Importance of the Infectobesity Field in More Effective Obesity Management

Tremendous progress has been made in infectobesity research, but social factors motivating the field are important considerations for appropriately prioritizing future research. Specifically, further understanding of viral etiologies could help counter obesity bias, reinforce public health approaches, and reinforce the value of biological science in the investigation of obesity.

First, public stigma against those afflicted with disease is often pervasive, particularly when there are physical manifestations (e.g., strabismus) [84]. With obesity, there are also behavioral causes, so bias is often more explicit. For instance, one scholar advocated increasing social pressure on people with obesity as a weight loss incentive [85]. However, those reporting perceptions of stigma gain more weight [86], while a socially supportive intervention improves hunger and eating behaviors [87].

Some suggest infectobesity sounds like a "lame excuse" for those who struggle with their weight [88], but biologic insight by itself should not remove the need for healthy behavior. To the contrary, providing information about personal obesity risk appears to increase healthy behavioral intentions regardless of how the causal pathway of the risk is described [89]. On the other hand, if infections were a more widely accepted factor in the development of obesity, an attributional justification for social stigma is reduced and more empathy and greater access to available treatments could follow.

Infectious etiologies of obesity also argue in favor of descriptions of obesity as an "epidemic" (or pandemic/endemic), even though these terms are often applied to characterize infectious diseases. More broadly, infectious etiologies have well established public health approaches for control. An important insight for human immunodeficiency virus treatment was that "treatment is prevention," suggesting that the whole population benefits when one case is medically treated [90]. Network dynamics also appear relevant for the spread of obesity, and these patterns could be used to prioritize obesity interventions [91].

Researching viral causes of obesity could lead to greater insight about the root causes of obesity within a biological framework related to host and agent adaptations. While obesity is multifactorial, oversimplification based on a physics-based thermodynamic model rather than a biological model has prevailed for over 90 years [92]. Both physics and biology have tremendous utility, but focusing on energy balance alone obscures the complex reasons for these behaviors and could limit the condition to the mathematics of these behaviors.

Some have advocated more tailored treatments for obesity subtypes that might respond differently to different treatments [93], and this also argues in favor of finding all the underlying etiologies, including infectious ones. Yet, current treatment of obesity is not cause-specific [93]. A recent example of an effective cause-specific intervention is the treatment of an obesogenic genetic defect, proopiomelanocortin deficiency, using melanocortin-4 receptor agonist [94] with excellent results.

Developing targeted antimicrobial agents or vaccines against microbes contributing to obesity could also be individualized. Spiramycin, an antibiotic used for toxoplasma in pregnancy [95], reduces adipogenesis in 3T3-L1 cells *in vitro* by reducing PPARγ and Glut-4 and ameliorating fat gain in mice on a high-fat diet [96]. This same pathway is activated by Ad-36, and this agent could be investigated as a targeted therapy for addressing obesity associated with viral infection.

Frameworks and Future Studies

Future investigation into infectobesity research gaps should carry a high priority. Several frameworks have been proposed to understand the causal role of infectious agents in human disease. Koch's postulates from 1890 still provide useful criteria for determining causal inferences, and some agents meet some of these postulates. However, in multifactorial diseases like obesity, it is unlikely that a single infectious agent is solely responsible for obesity. Any uninfected group used for comparisons may still develop obesity due to other contributors, including other microbes. Using pathogenic viruses to unequivocally determine causality in humans is generally impermissible from an ethical perspective (vaccine trials could be an exception).

In 2011, Dhurandhar proposed a more accommodating framework for identifying putative obesogen agents based on Ad-36, where three evidence categories (*in vitro*, animal, and human epidemiology) are used to draw obesogenic inferences [37•]. The framework is a valid starting point, and this review has focused on evidence from each of these three tiers for each category of virus reviewed. Since 2011, it has become clear that human epidemiology studies on this topic are difficult to interpret when considering a single virus in a randomly selected cohort for numerous, empirically supported reasons:

- Infection with one virus is non-randomly related to infection with other viruses because of co-infections, cross reactivity, host resistance, confounding, and/or other factors
- Many important adipogenic viruses likely have not been identified; only a handful of over 60 adenoviruses have been investigated, and many of the uninvestigated viruses are genetically similar and common in seroepidemiology studies [2•].
- Serostatus is not necessarily maintained over time, which has been documented for Ad-36 [97], so those without antibody at a given time point might still have had prior infection.
- Site and route of infection appear to make a difference in host phenotype for numerous infectious agents, and there is evidence they also matter for adipogenic viruses [14].
- Host factors appear to play a role in response to infection as empirically demonstrated using meta-regression on the association between Ad-36 and obesity among children and adults [20, 35]. Although significant in both populations, the magnitude of association is stronger in children (odds ratio [OR] = 2.3, $p < 0.001$ vs. OR = 1.8, $p = 0.005$) [20]. Insulin is involved in weight gain and weight loss, and a causal change in insulin sensitivity would be expected to promote weight gain in a naturalistic setting while promoting weight loss during a diet. Such an interaction by dieting status would be consistent with several empiric observations in longitudinal Ad-36 studies [55, 98, 99].
- There is high risk that the "Rose paradox" could play a role in observations at a population level because of host-agent interactions. That is, an individual might experience an inflammatory response to a particular virus and develop obesity even if the particular viral strain is not the most common cause of inflammation (or obesity) throughout the population.

These limitations suggest the need for carefully designed research with probative value [100]. To advance the field at a faster rate, we propose four specific priorities to make infectobesity research more comprehensive, leveraged, interventional, and patient centered.

Several new technologies exist that could enable more comprehensive assessment of potentially adipogenic agents, including metagenomic (agnostic) methods of next-generation sequencing and comprehensive virome characterization based on synthetic proteins [101]. Meta-genomics are necessary to identify phage, and thus far, we are not aware of any comprehensive assessment of phage and obesity correlation. Only within the last 3 years has meta-genomics characterized one of the most abundant biologic agents within the gut microbiome [102]. This tool could be applied to investigate agents in tissues outside the gut (e.g., liver, brain, or adipose tissue). Outcomes should also be assessed comprehensively as there can be beneficial or harmful adipogenic agents. For instance, E4-ORF1 may have beneficial properties for glucose disposal [50].

Other resources could also be leveraged such as emerging bioinformatics tools. We have previously leveraged pattern recognition to prioritize future investigation [2•]. Molecular basic research shows Ad-36 E4-ORF1 is necessary and sufficient for an adipogenic effect, and a public database (e.g., NCBI Blast) can be used to identify other viruses with nucleic acid homology for this gene. Comparison with seroepidemiology of adenoviruses allowed us to identify the agents with a similar gene and an abundant prevalence in population level studies. Likewise, bioinformatic tools may also predict tissue tropism, glycolytic/lipogenic genes, and inflammatory host response among common chronic viruses so that a more comprehensive catalog of potential adipogenic viruses could be identified and empirically validated.

Stronger causal inferences are possible with interventional studies and can be accomplished with emerging observational designs that incorporate an element of randomization [103], fully randomized platform trials [104], or traditional randomized clinical trials of vaccines. Even if many viruses contribute to obesity, recent vaccines have used polyvalent antigens (e.g., 9-valent HPV vaccine [105]) to create broad immunity. DNA viruses like adenoviruses in particular are readily vaccine preventable [106] since they have relative genomic stability [107] and a bivalent oral vaccine induced antibody with some cross protection to multiple adenovirus strains [108]. We proposed iterative selection and transfer of whole compartments of microbes to germ-free hosts in a process called pawnobe evolution [9••], which could allow causal inferences because transfers are interventions. With each transfer, any microbes within the compartment that confer an extreme phenotype should be selected and refined over time, and inferences about the microbial genetic changes responsible for these host traits could also be investigated as the microbes evolve.

Finally, future studies should be more patient centered. Many fields make progress after there is sufficient public interest in at least one application from the research. Some evidence suggests Ad-36 testing could help tailor a diet intervention because the Mediterranean diet is known to be more effective among the infected [98]. Similarly, gut microbe characterization has been used to tailor dietary recommendations with some utility [109]. Anti-inflammatory mulberry extract has been successful in treating mice with Ad-36 obesity, and it could plausibly counteract numerous sources of inflammation [58]. Combining a rigorous interventional design as described above with an anti-inflammatory therapy could provide faster translation to the patient than other novel basic science discoveries.

Conclusions

Overall, there is progress and persistent knowledge gaps in the infectobesity field. The theoretical and empirical support for

the biological plausibility of infectobesity has strengthened. There are shared patterns emerging with the five main categories of agents including inflammatory and endocrine pathways in the liver and adipose tissue. Additionally, the priorities for future investigation are becoming clearer. Focusing on early clinical interventions could expand the interest and opportunities for investigating the many questions related to infectobesity, while human epidemiology comes with numerous limitations.

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Compliance with ethical standards

Conflict of Interest Jameson D. Voss declares that he has no conflict of interest.

Nikhil V. Dhurandhar has several patents in viral obesity and adenovirus 36 including uses for E1A, E4-ORF1 gene and protein, and AKT1 inhibitor, and has ongoing grant support from Vital Health Interventions for determining anti-diabetic properties of E4-ORF1 protein.

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Papers of particular interest, published recently, are highlighted as:
- • Of importance
- •• Of significant importance

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