Background: Leptin, initially believed to simply be a satiety hormone responsible for obesity, is now recognized as a pleiotropic cytokine that is involved in many biological processes; including the body's host inflammatory response. Clinically, leptin may affect lung function although research in this area is limited. It is also known that the leptin receptor is necessary for the activation of the leptin protein, making it an important protein to consider. Furthermore, single nucleotide polymorphisms (SNPs) and DNA methylations of the leptin and leptin receptor genes (*LEP* and *LEPR* respectively) may provide important insight on the relationship that leptin has with inflammation in the body.

Objectives: This dissertation focused on: 1) the association between leptin and leptin receptor gene polymorphisms and lung function (forced vital capacity, FVC; forced expiratory volume in 1 second, FEV_1; and FEV_1/FVC) at ages 10 and 18. 2a) The association between *LEP* SNPs and *LEP* DNA methylation. 2b) The association between *LEP* DNA methylation and serum leptin levels. 3) The association between leptin and FVC, FEV_1, and FEV_1/FVC controlling for BMI.

Methods: The Isle of Wight (IOW) birth cohort, a population-based sample of 1,456 infants born between January 1989 and February 1990, was prospectively assessed at ages 1, 2, 4, 10, and 18 years. FVC, FEV_1, and leptin were collected at 10 and 18-year follow ups. SNP and DNA methylation data was analyzed from blood that was collected at birth and 18 years follow up respectively. Forty two independent repeated measurement analyses were conducted to test the association between *LEP* and *LEPR* SNPs and FVC, FEV_1, and FEV_1, FVC. Linear regression analysis tested the associated between *LEP* SNPs and *LEP* DNA methylation, as well as the association between *LEP* DNA methylation and serum leptin protein levels at age 18. Linear regression analysis was also used to the test the association between serum leptin levels at ages 10 and 18 and FVC, FEV_1, and FEV_1/FVC at ages 10 and 18.

Results: *LEPR* SNPs rs666354, rs1137101, and rs3762274 were associated with decreased lung function from ages 10 to 18. Those with the AC genotype of rs6669354 have 0.092 mL lower FVC and 0.10 mL lower FEV_1 than those with the AA genotype (Adjusted P-value=0.015 for both tests). A similar pattern was observed for SNPs rs1137101 and rs3762274 and the association with decreased FEV_1/FVC (Adjusted P-values 0.04 and 0.02 respectively). *LEP* SNPs rs11763517 and rs4731429 were both found to be associated with DNA methylation sites cg00666422 and cg24862443. *LEP* SNP rs4731429 was associated with cg00840332. The results were replicated in a second generation cohort. Increased methylation of cg00840332 interacting with rs11763517 and rs4731429 was associated with decreased serum leptin levels. Lastly, in boys, an increase in leptin levels from ages 10 to 18 was associated with 0.017 mL decreased FVC at age 18 (STD=0.007, P-value=0.018), while increased leptin between ages 10 to 18 was associated with FEV_1 at age 18 decreasing by 0.013 mL (STD=0.006, P-value=0.029). These association were seen even after controlling for body mass index (BMI).

Conclusions: *LEPR* SNPs are associated with decreased FVC, FEV_1, and FEV_1/FVC from ages 10 to 18. A possible mechanism for this association can be explained through the leptin protein. *LEP* SNPs are associated with *LEP* DNA methylation which in turn is associated with circulating serum leptin protein levels. And increase in leptin protein between the age of 10 and 18 is associated with decreased FVC in boys and decreased FEV_1 in girls at age 18.