“EFFECTIVENESS OF BEDTIME LEVOTHYROXINE INTAKE AS COMPARED TO STANDARD REGIMEN IN CHILDREN”

Dissertation submitted for

M.D., DEGREE EXAMINATION

BRANCH VII PAEDIATRIC MEDICINE

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN
MADRAS MEDICAL COLLEGE
CHENNAI
APRIL 2017

CERTIFICATE

This is to certify that the dissertation titled "**EFFECTIVENESS OF BEDTIME LEVOTHYROXINE INTAKE AS COMPARED TO STANDARD REGIMEN IN CHILDREN"** submitted by **DR. R.RADHAKRISHNAN** to the faculty of pediatrics, **THE TAMILNADU DR M.G.R MEDICAL UNIVERSITY, CHENNAI** in partial fulfillment of the requirements for the award of **M.D., DEGREE (PAEDIATRICS)** is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I **DR. R.RADHAKRISHNAN** solemnly declare that the dissertation titled **"EFFECTIVENESS OF BEDTIME LEVOTHYROXINE INTAKE AS COMPARED TO STANDARD REGIMEN IN CHILDREN"** has been prepared by me. This is submitted to the Tamil Nadu **DR.M.G.R Medical University,** in partial fulfillment of the rules and regulations for the M.D Degree examination in pediatrics.

Place : Chennai DR. R.RADHAKRISHNAN

Date :

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr. Radhakrishnan
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Dear Dr. Radhakrishnan,

The Institutional Ethics Committee has considered your request and approved your study titled **"EFFECTIVENESS OF BEDTIME LEVOTHYROXINE INTAKE AS COMPARED TO STANDARD REGIMEN IN CHILDREN" No. 14092015.**

The following members of Ethics Committee were present in the meeting held on **08.09.2015** conducted at Madras Medical College, Chennai-3.

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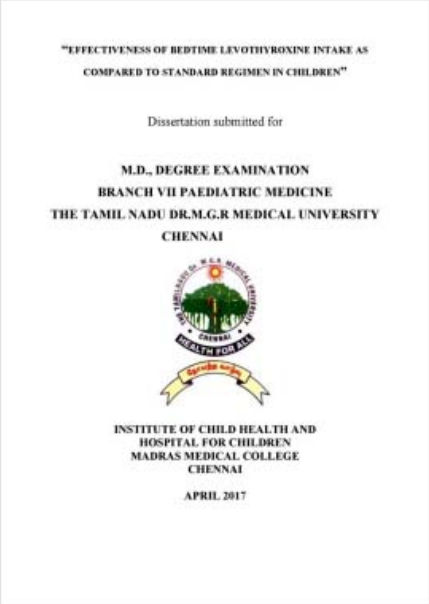

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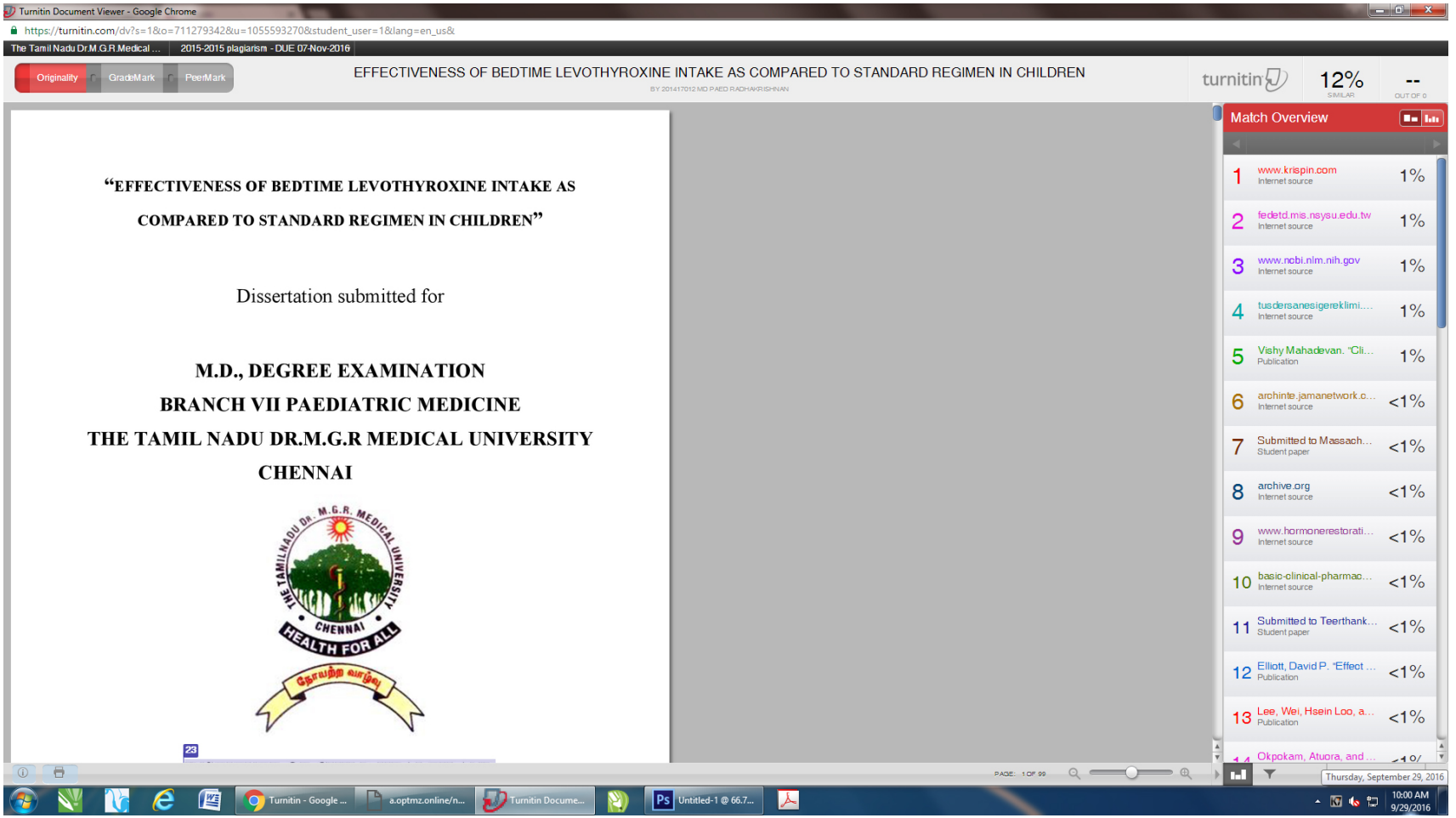
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Abbreviation

TSH	-Thyroid stimulating hormone
F T4	- Free T4
FSH	- Follicle stimulating hormone
LH	- Luteinizing hormone
HDL	- High density lipoprotein
BP	- Blood pressure
HR	- Heart rate

CONTENTS

INTRODUCTION

Hypothyroidism is a common endocrine disorder which results from deficiency of thyroid hormone. The nationwide programs for congenital hypothyroidism reported 1 in 4000 infant world wide . In endocrinology department of ICH&HC for children, madras medical college, chennai around 250 to 300 children are being treated for hypothyroidism. Hypothyroidism can be classified into

(1) primary hypothyroidism- due to defect in the thyroid gland itself.

(2) Hypopituitary Hypothyroidism (Central hypothyroidism) - due to decreased TSH production in pituitary gland, which may be due to defect in pituitary gland or due defect in hypothalamus (TRH deficiency).

Central hypothyroidism usually presens as multiple congenital pituitary hormone deficiency.

Hypothyroidism may be present since birth (congenital) or it may present late (acute). Levo-thyroxine is used in treatment of both congenital and acquired hypothyroidism. Levo-thyroxine commonly used because of its stability, content uniformity, low cost, lack of allergenic foreign proteins and long half life which allow once daily administration.

Compared to Levo-thyroxine, Liothyronine(T3) is three to four time more potent but it is not recommended for routine replacement therapy because of its shorter half life (24Hrs) which needs multiple daily dose, higher cost and difficulty in monitoring adequacy of replacement. Liothyronine is used as intravenous preparation in emergency condition of myxedema coma.

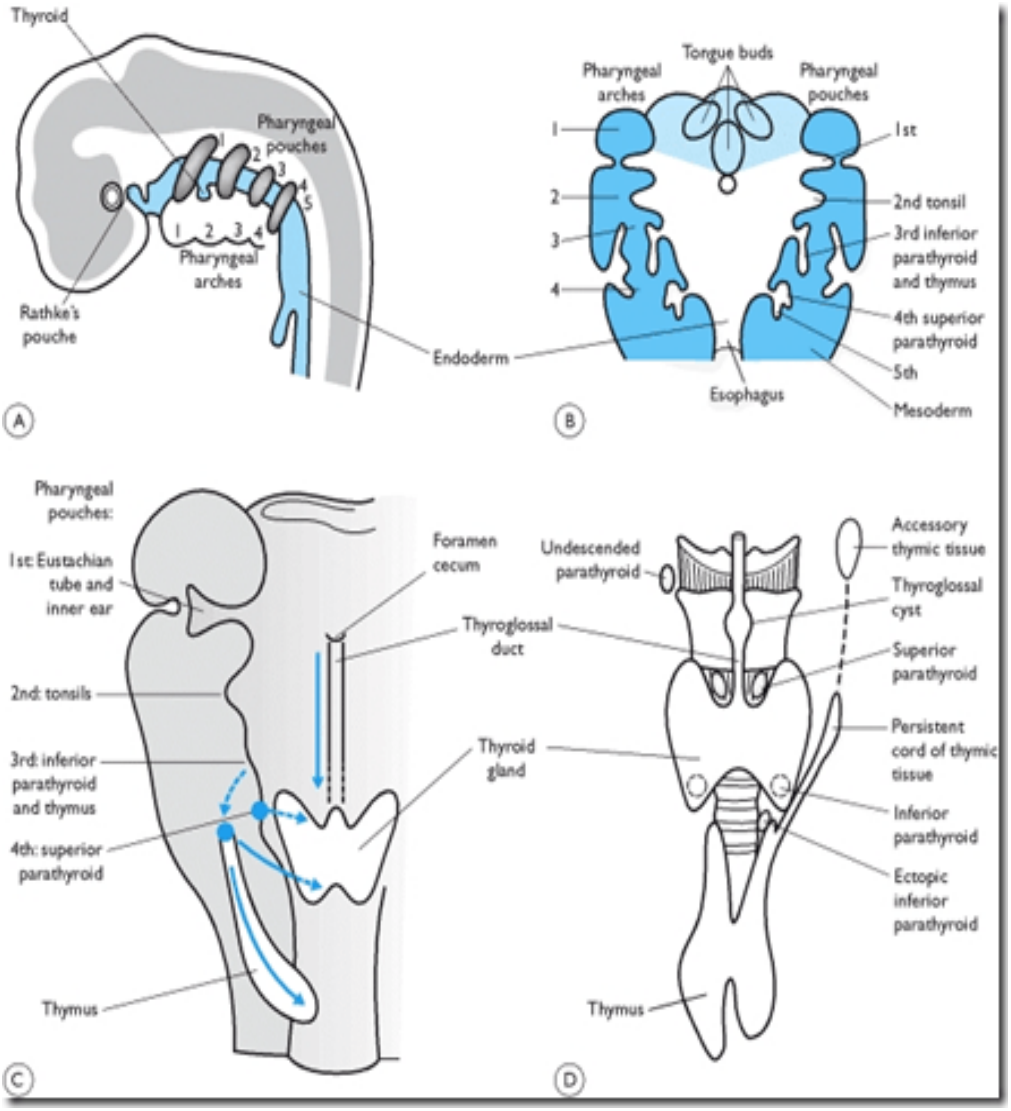
Normally Levo-thyroxine is given in morning empty stomach 30 to 60 minutes before breakfast as its adsorption is influenced by the food. In previous pilot study changing of Levo-thyroxine regimen from morning to evening time has improved the TSH level.

THYROID GLAND

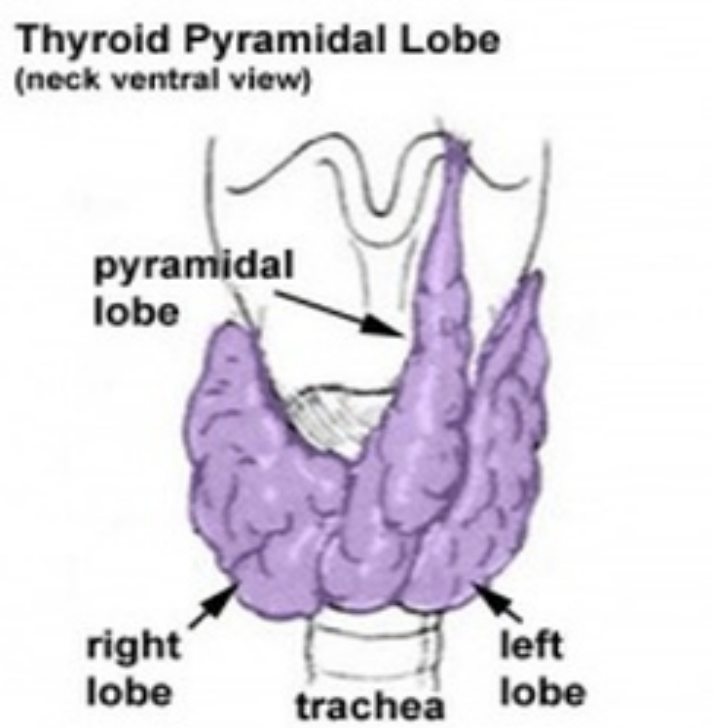
Thyroid is a meticulous gland.

Embryology

Thyroglossal duct gives rise to the thyroid. Tuberculum impar is a midline swelling present in the medial end of first pharyngeal arch (mandibular arch). The epithelium of floor of the pharynx just behind the tuberculum impar shows a thickening in the midline and soon gets depressed below the surface to form a diverticulum called the thyroglossal duct. Foramen caecum is the name given to the site of origin of diverticulum. Thyroglossal duct grows down in the midline into the neck. The tip of diverticulum bifurcates and gives rise to the two lobes of thyroid gland.



Thyroid gland situated in the lower part of the front and sides of the neck. Thyroid gland consists of right lobe and left lobe which are joined to each other by the isthmus. Pyramidal lobe is a third lobe which projects upwards from the isthmus or from one of the lobes. Levator of the thyroid gland is a fibromuscular band which descends from the body of the hyoid bone to the isthmus or to the pyramidal lobe. Accessory thyroid glands are small detached masses which contain thyroid tissue sometimes found in the vicinity of the lobes or above the isthmus.



The vertebral level of thyroid gland is C5, C6, C7 & T1. Each lobe extends from the middle of the thyroid cartilage to the fourth or fifth tracheal ring. The extent of isthmus is from second tracheal ring to fourth tracheal ring

Thyroid gland is surrounded by two capsules. The true capsule is the inner layer which is the peripheral condensation of the connective tissue of the thyroid gland. A dense capsular plexus is present deep to the true capsule. The capsule is derived from the pretracheal layer of deep cervical fascia. The suspensory ligament of berry is thick part of false capsule present in inner surface of the gland which connects the lobes to cricoid cartilage .

Isthmus is occasionally absent in some individual. The anterior surface of isthmus is covered by sternothyroid muscle, sternohyoid muscle, anterior jugular vein, fascia and skin. Posterior surface of isthmus lies over second and fourth tracheal rings. Inferior thyroid vein leaves the lower border of the

isthmus. The anastomosis between the right and left superior thyroid arteries is related to the upper isthmus border.

The right and left thyroid lobes are conical in shape. Lobes are divided into apex, base, lateral surface, medial surface, posterolateral surface, right border and left border. The isthmus is divided into anterior and posterior surface with superior and inferior border.

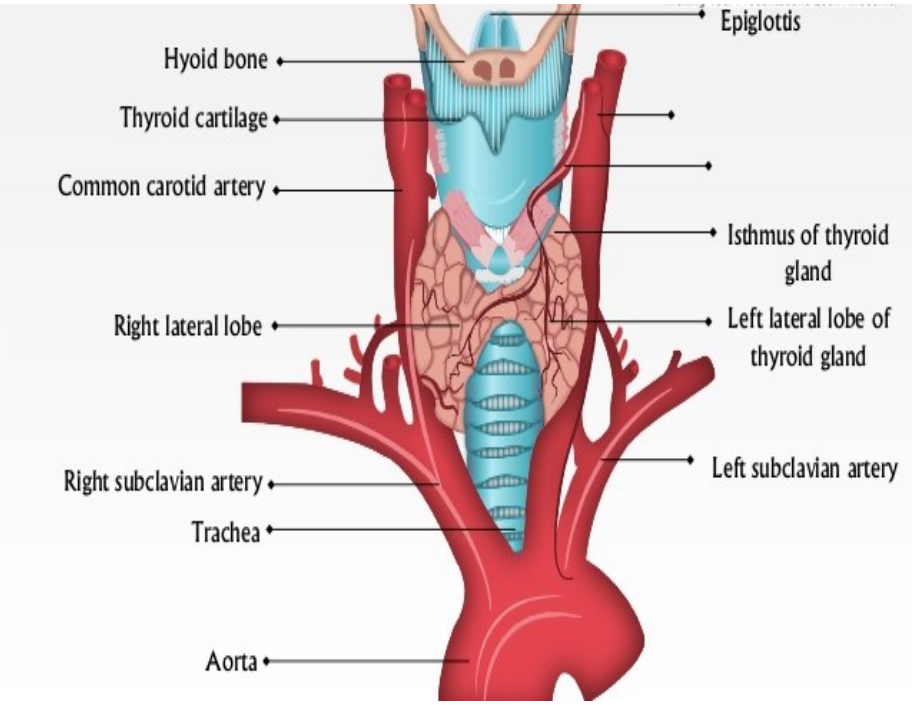
The apex of each lobe is directed upwards and laterally which is limited by the attachment of the sternothyroid muscle to the oblique line of the thyroid cartilage .

The base of each lobe occupies the 4^{th} or 5^{th} tracheal ring . The anterior border is thin and posterior border is thickened and rounded. Posterior border separates the medial and posterior surfaces. The inferior thyroid artery is related to posterior border and superior thyroid artery is related to anterior border. The parathyroid gland and the anastomosis between superior and inferior thyroid arteries are related to posterior border of thyroid lobes. The posterior border of the left lobe is related to thoracic duct.

There are three surfaces for each lobe. Lateral surface also known as superficial surface is convex one and covered by the muscles sternohyoid, superior belly of omohyoid, sternothyroid, anterior border of sternocleidomastoid. Trachea and esophagus are related to medial surface of each lobe. Medial surface is also related to inferior constrictor, cricothyroid, external laryngeal nerve and recurrent laryngeal nerve. The posterior or

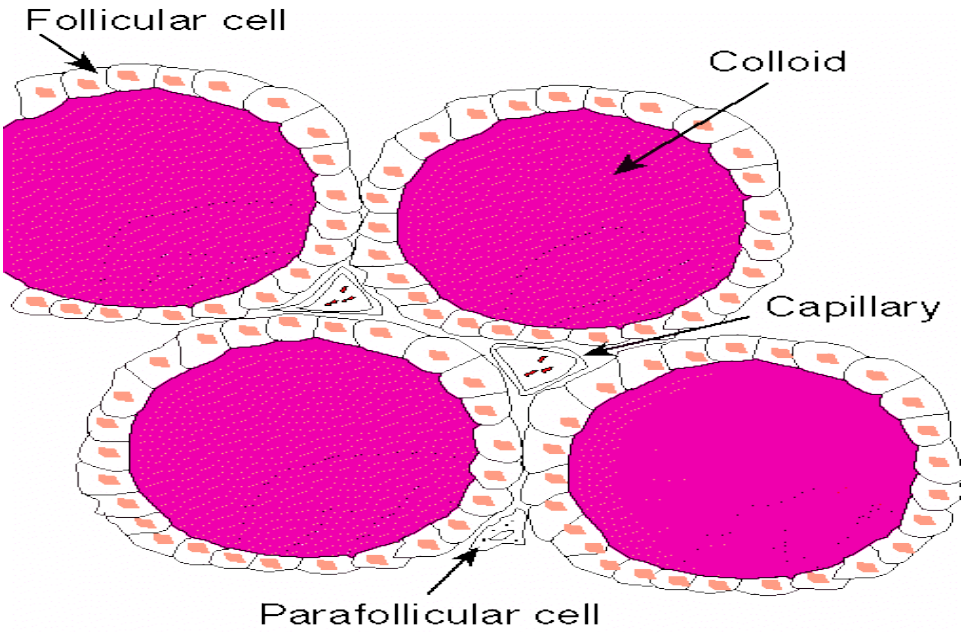
posterolateral surface is related to carotid sheath and overlaps the common carotid artery.

Superior thyroid arteries and inferior thyroid arteries are the major blood suppliers to thyroid gland. The superior thyroid artery divides into two branches the anterior and posterior branch. The division occurs when the artery pierces the pretracheal fascia, before which it gives branches to adjacent structures while originating from external carotid artery. The anterior branch of superior thyroid artery descends over the anterior border of the lobe and continues along the upper border of isthmus to anastomose with its fellow of the opposite side. But the posterior branch anastomoses with the descending branch of the inferior thyroid artery. The inferior thyroid artery is a branch of the thyrocervical trunk. It passes behind the carotid sheath and the middle cervical sympathetic ganglion and in front of the vertebral vessels. The terminal branch is related to the recurrent laryngeal nerve. Before entering the gland, the artery divides into four to five glandular branches which pierce the fascia separately. Ascending branch of inferior thyroid artery supplies the parathyroid gland and anastomoses with the posterior branch of the superior thyroid artery. About three percent of individuals have blood supply from thyroid ima artery which is arises from the brachiocephalic trunk or directly from the arch of aorta. The thyroidea ima artery is also called lower thyroid artery. Accessory thyroid arteries from tracheal and esophageal arteries, also supply the thyroid gland.



Three veins namely superior, middle and inferior thyroid veins drain the thyroid gland. The superior thyroid vein accompanies the superior thyroid artery, which emerges at the upper pole and drains either in the internal jugular vein or in the common facial vein. The middle thyroid vein is a short and emerges at the middle of the thyroid lobes and drains into internal jugular vein. The inferior thyroid vein emerges at lower border of isthmus and form a plexus in front of the trachea and drains into the left brachiocephalic vein. Vein of kocher, a fourth thyroid vein is an inconsistent one which may emerge between the middle and inferior veins and drain into the internal jugular vein.

Nerve supply of the thyroid gland is mainly from the middle cervical ganglion and also partly from superior and inferior cervical ganglia.



Histology of thyroid

Thyroid gland is divided into lobules. Each lobules consists of 20 to 40 round to oval follicle, each measures about 50-500 micron with single layer of cuboid to low columnar epithelium . The hormone is present within the cavity surrounded by secretary cell which make up a follicle. The lumen contains colloid which is pale during active secretion , densely eosinophilic during inactive stage and more flocculent and basophilic in elderly. “C” cell occupies the 0.1% of the gland

THYROID HORMONE

Thyroxine (T4) and Triiodothyronine (T3) are produced by the thyroid follicles and have similar biological activity.

CHEMISTRY AND SYNTHESIS

Both the hormones are iodine containing derivatives of thyronine. They are stored in the thyroid follicles bound to the thyroglobulin molecule.

Synthesis involves the following processes

IODINE UPTAKE:

Under the stimulation of TSH thyroid cells trap iodine by an active transport process which is mediated by Na^+ : I^- symporter. An uptake gradient more than 100 fold is present.

OXIDATION AND IODINATION:

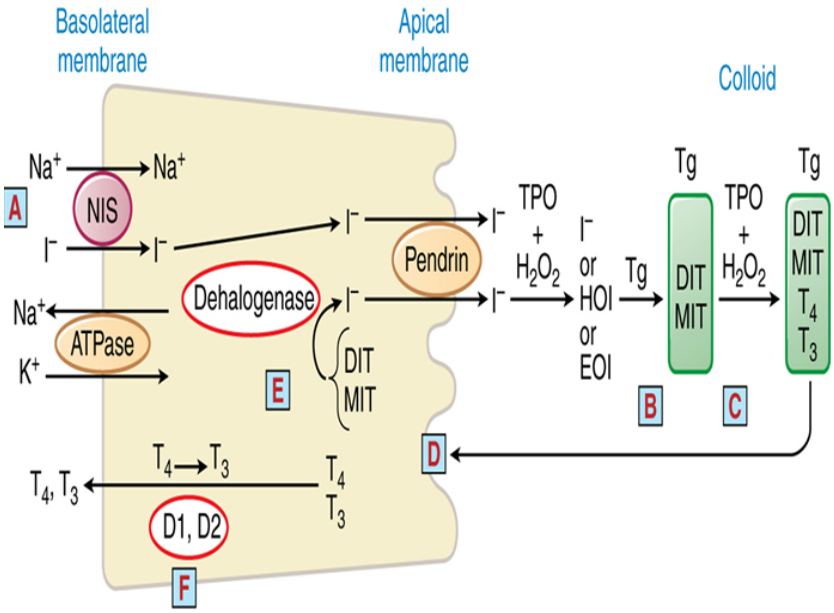
The trapped iodine is then carried across apical membrane by pendrin and oxidized to iodinium (I^-) ions by thyroid peroxidase enzyme or to hypoiodous acid (HOI) or enzyme linked hypoiodate (E-OI) with the help of H2O2. These forms combine with tyrosil residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).

COUPLING:

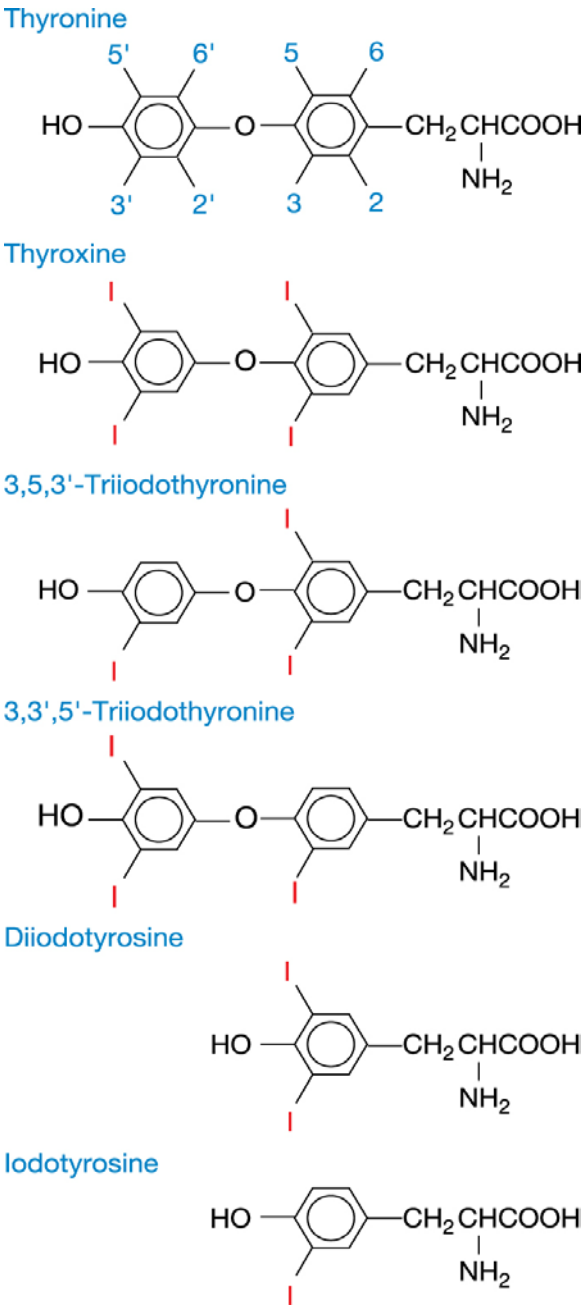
Under the catalysis of thyroid peroxidase, iodinated tyrosil residues couple to form T3 and T4. Normally more T4 than T3 is formed , but in Iodine deficiency state more MIT is available and more T3 is formed.

STORAGE AND RELEASE:

Iodinated tyrosil residues are stored as colloids in the interior of the follicles. Hydrolysis of the thyroglobulin leads to release of free T3 and T4 and MIT & DIT is the next step. Then the later are deiodinated to give raise to iodide and it is reused by the thyrocyte.



KEY		
	METABOLIC STEP	INHIBITOR
A	Iodine transport	ClO_4^-, SCN
B	Iodination	PTU, MMI
C	Coupling	PTU, MMI
D	Colloid Resorption	Colchicine, Li^+, I^-
E	Deiodination of DIT + MIT	Dinitrotyrosine
F	Deodination of T_4	PTU



Thyroid hormones are transported in the serum bound to thyroxine binding globulin (TBG), thyroxine binding pre albumin (TPBA) and albumin. Only a small amount of T4 (0.03%-0.08%) and T3 (0.2%-0.5%) is free , and it is physiologically active. 99.98% of the T4 and 99.8% of T3 is in bound form. T3 is 3 to 4 times more potent than T4. The T3 is less tightly bound to

protiens, hence the circulating levels are much lower than T4. It enters the tissues more easily. Half life of T3 is one day while half life of T4 is seven days. Normal T4 : T3 secretion in human thyroid is 11:1.

Factors that Alter Binding of Thyroxine to Thyroxine-Binding Globulin

INCREASE BINDING	DECREASE BINDING
Drugs	
Estrogens	Glucocorticoids
Methadone	Androgens
Clofibrate	L-Asparaginase
5-Fluorouracil	Salicylates
Heroin	Mefenamic acid
Tamoxifen	Antiseizure medications (phenytoin, carbamazepine)
Selective estrogen receptor modulators	Furosemide
Systemic Factors	
Liver disease	Inheritance
Porphyria	Acute and chronic illness
HIV infection	
Inheritance	

The condition that cause increased TBG site there is shift of hormone from free site to bound site so there is increase in total and bound hormone but no changes in free hormone ,decrease in rate of elimination. When TBG site decreases reverse will occur.

T4 is entirely released by thyroid gland while only 20% of T3 is released by thyroid gland, and the remaining 80% of T3 is produced by de-iodination of T4 in liver, muscles and kidneys.

Metabolism and excretion of thyroid hormone:

The metabolic inactivation of T4 and T3 occurs in the liver, kidneys and salivary glands. Glucuronide / sulfate conjugation and de-iodination occurs and then they are excreted in bile. In the intestines a major fraction is deconjugated and reabsorbed into entero hepatic circulation and finally excreted in urine. Recommended iodine intake 90-120micrograms per day. Iodine present in food, water and medication. Thyroid gland requires 75 microgram per day for thyroid hormone synthesis, remaining amount of iodine excreted in urine. Increased metabolic clearance and decreased half life of thyroid hormone occurs in hyperthyroidism, decreased metabolic clearance and increased half life of thyroid hormone occurs in hypothyroidism. T4 converted to T3 by iodothyronine de-iodinase. Deiodinase enzymes are of three different varieties namely D1, D2 and D3. The three enzymes have a common aminoacid selenocystine which is a rare aminoacid which adds uniqueness to thyroid system.

D1- liver,kidneys ; peripheral conversion of T4 to T3

D2 – brain , pituitary ; production of T3

D3 – brain; production of RT3

Properties of Iodothyronine Deiodinases			
	TYPE 1 (D1)	TYPE 2 (D2)	TYPE 3 (D3)
Outer ring deiodinase	Yes	Yes	No
Inner ring deiodinase	Yes	No	Yes
Inhibited by PTU	Yes	No	No
Inhibited by amiodarone	Yes	Yes	Unknown
Regulation by thyroid hormone	T_3 induces D1 gene expression	Substrate (T_4) causes D2 protein degradation	T_3 induces D3 gene expression
Location	Liver, kidney, thyroid, pituitary	Brain, pituitary, hypothalamus, thyroid, brown fat, skeletal muscle (very low levels)	Brain, placenta, some sites of inflammation
Selenocysteine in active site	Yes	Yes	Yes

TSH:

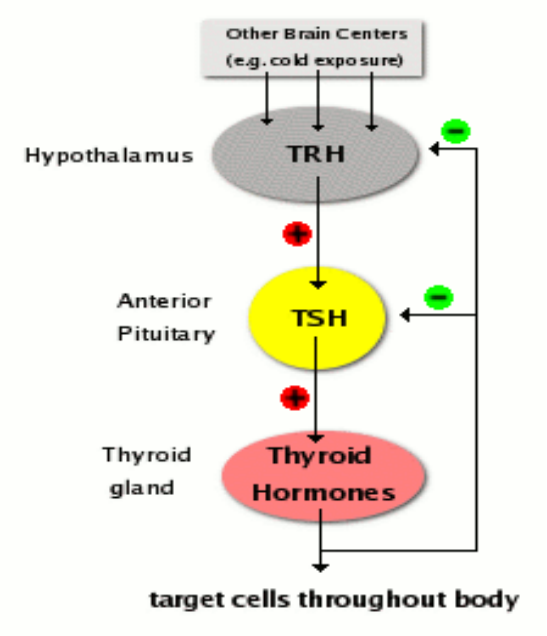
TSH is a glycoprotein containing 211 amino acid residues. It consists of one alpha and one beta sub unit encoded by genes on chromosome 6 and 1 respectively. TSH alpha is identical to the alpha sub unit of other pituitary hormones namely LH ,FSH , hCG-alpha and the specificity of TSH is conferred by the beta sub unit. Half life of TSH is 60 minutes and mostly degraded in kidneys and lesser amounts in liver. TSH exerts its action through TSH receptor which is a G protein coupled receptor.

Regulation :

Thyroid hormone secretion is regulated by pituitary hormone Thyroid Stimulating Hormone(TSH) which in turn is controlled by hypothalamic Thyrotropin Releasing Hormone(TRH).

Maintenance of normal thyroid secretion is due to the feedback interplay of thyroid hormones with TSH and TRH. TRH stimulates pituitary TSH which stimulates thyroid gland to secrete T3 and T4. High level of T3 and T4 by a

negative feedback mechanism suppress TSH and TRH secretion there by reduces thyroid hormone synthesis. Stress has a inhibitory effect on TRH. Dopamine and Somatostatin inhibit TSH secretion.



Mechanism of action:

T3 penetrates the cells and combines with the specific DNA sequences called " thyroid hormone response element" over the nuclear receptor which leads to suppression or direct activation of gene transcription resulting in expression of predetermined pattern of protein synthesis. By sensitization of adrenergic receptors to catecholamines,many of the clinical manifestations of thyroid hormones like tachycardia, arrhythmias, hypertension, hyperglycaemia, tremor occurs. Throid receptor genes is of two types alpha and beta. Alpha encoded by a gene on chromosome 17 and beta on chromosome 3. TRbeta2 is found only in brain while TRalpha1, TRalpha2 , TRbeta1 is widely distributed. The complexity of mechanisms involved in action of thyroid

hormone at nuclear level explains the ability of thyroid hormones to produce a variety of biologic actions.

Pharmacokinetics:

Thyroxine is absorbed in stomach and small intestine but best absorbed in duodenum and ileum. Absorption influenced by the food ,various drugs, gastric acidity and intestinal flora. Oral bioavailability of levo-thyroxine is 60-80% due to relation with food intake.T3 oral bioavailability is 95%.

Factors Influencing Oral Levothyroxine Therapy

Drugs and other factors that may increase levothyroxine dosage requirements
- *Impaired levothyroxine absorption*
  - Aluminum-containing antacids
  - Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
  - Calcium carbonate (effect generally small)
  - Chromium picolinate
  - Food
  - Iron salts
  - Lactose intolerance (single case report)
  - Phosphate binders (lanthanum carbonate, sevelamer)
  - Proton pump inhibitors
  - Raloxifene
  - Soy products (effect generally very small)
  - Sucralfate
- *Increased thyroxine metabolism, CYP3A4 induction of hepatic*
  - Bexarotene
  - Carbamapzepine
  - Phenytoin
  - Rifampin
  - Sertraline
- *Impaired $T_4 \rightarrow T_3$ conversion*
  - Amiodarone
- *Mechanisms uncertain or multifactorial*
  - Estrogen pregnancy
  - Ethionamide
  - Tyrosine kinase inhibitors (imatinib, sunitinib)
  - Lovastatin, simvastatin

Drugs and other factors that may decrease levothyroxine dosage requirements
- Advancing age (>65 years)
- Androgen therapy in women

Drugs that may decrease TSH without changing free T_4 in levothyroxine-treated patients
- Metformin

THYROID HORMONE FUNCTIONS

Thyroid hormones affect almost every system in the body.

Growth and development

Thyroid hormones exert a critical control over protein synthesis. Thyroid hormone deficiency affects mainly the nervous system in early fetal life. In cretinism there is mental retardation and neural deficit due to paucity of synaptic formation, dendritic and axonal ramification and reduced myelination. Overt hypothyroidism in the adult causes impairment of intelligence and slow movements.

Carbohydrate Metabolism:

Thyroid hormones stimulate carbohydrate metabolism. Though the utilization of carbohydrates is raised, Basal Metabolic Rate (BMR), glycogenolysis& gluconeogenesis in Liver as well as faster absorption of glucose compensate for it. In hyperthyroidism there is a state of hyperglycaemia with diabetic like state.

Protein Metabolism:

The effect of T4 over the proteins is catabolic. Prolonged action results in negative nitrogen balance and tissue wasting. Hence there is loss of weight in hyperthyroidism. Mucoprotein synthesis is inhibited by thyroid hormones. Due to loss of inhibition they accumulate and causes myxedema and hence weight gain occurs in hypothyroidism.

Lipid Metabolism:

Though lipogenesis is also stimulatedT3 and T4 enhance lipolysis through potentiating action of other hormones. Many phase of metabolism of Cholesterol is accelerated, though its conversion to bile acids dominates. Hence there is hypocholesterolemia in hyperthyroidism and obesity & hypercholesterolemia in hypothyroidism.LDL levels in blood are also reduced.

Calorigenesis:

BMR is raised by stimulating cellular metabolism and resetting the energystat level. But BMR in gonads, uterus, spleen, brain and lymph nodes is not significantly affected. Uncoupling of oxidative phosphorylation results in release of excess energy as heat.

Cardio vascular system:

Contractility, heart rate, and cardiac output are all increased which results in fast & bounding pulse. Upregulation of beta adrenergic receptors by thyroid hormones results in positivechronotropic and inotropic effect . Effects of catecholamines are augmented, hence atrial fibrillation, arrhythmias, and angina are more common in hyperthyroidism. Systolic blood pressure is often raised.

Nervous system

Thyroid hormones are essential for CNS maturation. Thyroid hormones maintain the normal hypoxic and hypercapnic drive of the respiratory centre in the brain. There is mental retardation in cretinism. Tremors,hyperreflexia, & anxiety are seen in hyperthyroidism whereas sluggishness is seen in hypothyroidism.

Skeletal muscle

T3&T4 increase the protein metabolism resulting in increased speed of muscle contraction and relaxation. Thus muscle weakness is seen in myxedema and tremor, increased muscle tone is seen in thyrotoxicosis.

Gastro intestinal system

T3&T4 increase gastric motility. Constipation is seen in hypothyroidism while diarrhoea is seen in hyperthyroidism.

Haemopoiesis:

Anaemia occurs in hypothyroid patients hence it is proven that thyroid hormones play a role in haemopoiesis.

Reproduction:

Hypothyroid women have oligomenorrhea& infertility. Hence it is proven that thyroid hormones are essential for the maintenance of pregnancy and lactation.

Target Tissue	Effect	Mechanism
Heart	Chronotropic Ionotropic	Increased number of adrenergic receptors
		Enhanced responses to circulating catecholamines
		Increased proportion of myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary)
		Increased metabolic rate

USES OF THYROXINE:

a) Cretinism

b) Non toxic goitre

c) Myxoedema coma

d) Adult hypothyroidism

e) Thyroid nodule

f) Papillary carcinoma of thyroid

ADVERSE EFFECTS :

The unwanted effects of thyroid hormone is related to their physiologic function and include

1. Cardiac dysrhythmia
2. Angina
3. Congestive cardiac failure

Lid lag , eyelid retraction , excessive sweating , tremor, restlessness , heat intolerance, diarrhoea and other effect of hyperthyroidism are dose dependent toxic effect of this hormone. Chronic excess of thyroid hormone lead to osteoporosis.

Thyroid hormone preparation :

Synthetic preparation of sodium salts of the natural isomer of the thyroid hormone are as follows

1. Levothyroxine is available in tablet and powder form for injection. Tablet form used for daily maintenance dose. Follow up blood testing typically are done 6 weeks after any dosage changes because of its plasma half life is 1 week.
2. Liothyronine - salt of triiodothyronine. It is available in tablet and injectable form. When more rapid onset of action or rapid

termination is desired, liothyronine is indicated because its half life is 1 day. Peak serum level following oral intake occurs in 2 to 4 hours.

3. Other preparations - mixture of thyroxine and triiodothyronine is available in ratio of 4:1.

ASSESMENT OF THYROID FUNCTION

Thyroid function can be assessed by levels of serum TSH ,free T3&T4 and total T3 &T4.

TSH is most sensitive indicator of primary hypothyroidism and not useful in central hypothyroidism.

T4 level is better indicator than T3 due to increased peripheral conversion in thyroid depleted states. Estimation of free thyroid hormone is superior to total hormone due to variability in levels of thyroid binding globulin.

Low free T4 and TSH levels indicates Central hypothyroidism.

High TSH indicates primary hypothyroidism.

Persistent elevation of TSH and normal free T4 indicates Subclinical hypothyroidism.

Elevated FT4 and undetectable TSH indicates Hyperthyroidism.

HYPOTHYROIDISM

Decreased thyroid hormone has significant impact on growth and development.Untreated congenital hypothyroidism leads to devastating

intellectual and developmental consequences.Acquired hypothyroidism affects growth and school performance.

Etiology

Hypothyroidism can be caused by defects in hypothalamus –pituitary axis,thyroid gland or peripheral sensitivity to thyroxine.

Primary causes (Thyroid)

- Autoimmune thyroiditis
- Enzyme defects: Trapping, Organification, Thyroglobulin synthesis, Deiodination
- Iodine deficiency:Endemic goiter
- Dysgenesis: Aplasia, dysplasia, ectopic
- Thyroid injury :Surgery, Radiation , Infection
- Goitrogens : Thiocyanates, Iodine ,Amiodarone
- Transient :Maternal TSH receptor blocking antibody, maternal antithyroid drug.

Secondary or Tertiary (Hypothalamus or Pituitary)

- Malformations : septo optic dysplasia, holoprosencephaly
- Genetic defects
- CNS insults : Trauma , surgery, radiation, infection
- CNS tumors :Craniopharyngioma , germinoma
- Peripheral (Extremely rare)
- Resistance to thyroxine

Clinical features of Hypothyroidism

CONGENITAL	ACQUIRED
Open Posterior fontanelle	Growth retardation
Umbilical Hernia	Delayed skeletal maturation
Characteristic edematous facies	Delayed Dental development
Constipation	Delayed Puberty
Pallor	Myopathy and Pseudohypertrophy
Hypothermia	Enlarged Sella
Large tongue	Pseudotumor cerebri
Rough dry skin	
Hypotonia	
Large Abdomen	

Recommended dose of Thyroxine

AGE	LEVOTHYROXINE DOSAGE (mcg/kg)
0-3 mths	10-15
3-6 mths	8-10
6-12 mths	6-8
1-3 yrs	4-6
3-10 yrs	3-4
10-15yrs	2-4

ETIOLOGY OF HYPERTHYROIDISM

Infancy

- Transplacental transfer of thyroid antibodies
- TSH receptor activating mutation

After Infancy

- Grave's disease
- Subacute thyroiditis
- Toxic thyroid nodule , Toxic multinodular Goitre

Iatrogenic

- Pituitary resistance to T3

REVIEW OF LITERATURE

Nienke bolk et al[1] conducted a randomized double-blind crossover trial in Netherlands to evaluate the effects of evening versus morning Levothyroxine intake,105 patients with primary hypothyroidism were enrolled for the study. Patients were followed up for 6 months during which instructions were given to take 1 capsule in the early morning empty stomach and 1 capsule at night 2 hour after dinner (one tablet contained levothyroxine and the other a placebo), patients were advised a switch after 3 months. Primary outcome of the study was estimating thyroid hormone levels; secondary outcome was to measure serum creatinine and lipid levels, change in body mass index, heart rate, and quality of life.

Total of 90subjects completed the trial and results were analyzed. Authors observed a significant fall in TSH concentration of 1.25mIU/L (95%CI 0.60-1.89 mIU/L; p< .001) when levothyroxine was taken in bed time when compared with morning intake, similarly they also observed significant increase in free thyroxine level of 0.07 ng/dL (95% CI 0.02-0.13ng/dL; P = .01) and significant increase in concentration of total triiodothyronine of 6.5ng/dL (95% CI 0.9-12.1ng/dL; p = .02) when levothyroxine was administered during night time. Secondary outcomes did not show significant changes between morning versus night time intake of levothyroxine.

Authors concluded that bedtime intake of levothyroxine will significantly improve thyroid hormone levels.

Shivshankar et al[2] did a study tom evaluate the effect of levo-thyoxine intake 45-60 minutes before the breakfast on elevated TSH levels.

To analyze the effectiveness of above change 10 patients with hypothyroidism were enrolled which included 9 female and 1 male individual. Median age was 39 years, median duration of hypothyroidism 6 years, serum free T4 : 13pmol/L and TSH 12.63mIU/L. These subjects were advised to take levo thyroxine 45-60 minutes prior to breakfast or other oral medications.

After two months all 10 patients show biochemical improvement with decreased mean TSH and increased free T4 values. Compared to baseline values (TSH 12.63(6.2-48.3)), free T4(13(10.5-17.1)) after 2 months show following improvement TSH (3.15(0.04-6.8)) , free T4(17.7(14-21.3)) that is statistically significant(p value <0.05 and p value <0.01) respectively. Changing the levothyroxine 45 – 60 minutes before breakfast and other medication reduce the TSH level by 40 to 96 % in all patients. We advised to all patients to follow the protocol.

T-G bach-huynh et al[3] did a randomized double-blind crossover study to evaluate the effect of timing of Levothyroxine administration in relation food on serum thyrotropin concentration.

Individuals taking levo-thyroxine treatment for hypothyroidism or thyroid malignancies were selected as study participants. Among 84 individuals who were willing to participate, 65 completed the study.

Three-period cross over study was designed. Primary outcome was to evaluate the difference between serum TSH concentration in fasting state and

during other 8 week regimen. Individuals were randomized to one of the six sequences. Each sequence consisted of three eight week regimen. The regimens were fasting state, bed time and with breakfast. TSH, free T4, and total T3 concentrations were measured during each regimen.

65 patients completed the study. Authors found that mean TSH concentration when levo-thyroxine administered in fasting state (1.06 ± 1.23 mIU/L) was significantly low when compared to TSH levels when levothyroxine was taken with breakfast(2.93± 3.29 mIU/L) and during bedtime(2.19 ± 2.66 mIU/L).

They concluded that levo-thyroxine intake in fasting state ensures to maintain TSH levels within the target range and levothyroxine in non-fasting state is associated with higher and varying levels of TSH.

Studies also demonstrate that optimal absorption of levo-thyroxine during fasting condition was 80% and it decreases to 40-64% with food intake..

Rajesh Rajput et al[4] conducted a study to evaluate the effect of morning against Evening levothyroxine in treatment of hypothyroidism.

152 newly detected primary hypothyroid individuals were enrolled for the study. This population was divided into two groups. Group 1: morning dose of levothyroxine in empty stomach (n=77). Group 2: night dose of levothyroxine 2hours after dinner (n=75). These subjects were followed up for a period of 12 weeks. Improvement in Quality of life, clinical profile and biochemical parameters were assessed at baseline, 2 , 6 and 12 weeks.

Authors found that 90.90% of group 1 subjects and 96% of group 2 subjects attained euthyroidism at the end of 12 weeks of observation period. Group 2 attained euthyroidism early when compared to group 1, however it was not statistically significant. In both the groups clinical symptoms, clinical scores and thyroid profile showed significant improvement at the end of 6 and 12 weeks. No significant difference was noted in thyroid profile between two groups upon intergroup comparison at 6 and 12 weeks. And in both groups similar dose of levo-thyroxine was used to achieve euthyroidism. Authors concluded that " evening dose is as efficacious as morning dose and may provide an alternate dosing regimen."

Ala S et al[5] conducted a study to find out the effect on levels of TSH and T4 due to change in administering levothyroxine from before breakfast to before dinner.

50 hypothyroid patient was included in the study and were divided into two groups. Both group received two tablets (one containing levothyroxine and another containing placebo) one before breakfast and another one before dinner. 2months later time of tablet administration was changed for both group, and was continued for another 2 month. Serum levels of TSH and T4 was measure in each group before start of study, at 2 month and completion of study.

Authors found that by changing time of administering levothyroxine TSH level significantly increased by 1.47±.51µIU/ml with P value of 0.001 and T4 level reduced by 0.35±1.05µg/dl with P value of 0.3. Authors concluded

that changing the timing of administering levothyroxine from before breakfast to before dinner minimally reduced the therapeutic efficacy of levothyroxine. In patient who are taking exogenous levothyroxine, it is reported that higher total and free serum thyroxin level can be seen than in euthyroid controls. This can be due to artifact of the serum sample collection time.

Ain KB et al[6] did a study to find out the effect of serum sample collection time on thyroid hormone levels in patient taking levothyroxine therapy for replacement(26 patient)and for suppression of thyrotropin(25 patient).

Blood samples were collected during regular clinic visits (random sample), and following more than 22 hours of levothyroxine intake(trough sample).Total and free thyroxine, triiodohyronine, and thyrotropin level were assessed .

Authors found that "Random sample had increased total thyroxine levels in patient receiving replacement(8.1±1.2%,mean ±SE,P = 0.0001)and patient receiving suppression therapy(8.8±1.6%,P =0.0001) as compared to corresponding trough sample". Free thyroxine was increased by 12.7±2.6 %,(P =0.0003)

Pilot study conducted by **Bolk N et al**[7] Objective: Standard pharmacology textbook recommends that levothyroxine should be ingested 30 to 60 minutes before breakfast in empty stomach to decrease the interference of food with drug absorption. They observed changing of levothyroxine schedule

from fasting to late evening to decrease in TSH levels. so they planned for pilot study to analyse the change of levothyroxine at bed time

12 primary hypothyroid women treated with levothyroxine included in study.patient were instructed to take morning dose of thyroxine regularly, two months later patients were switched to night dose, same dose of levothyroxine was used. Patients were tested for two times, first time on stable regimen morning thyroxine intake, second time two month after switching to night.

Patient was admitted in hospital for 24 hour, blood withdraw was done hourly for 24 hour. After 2 month of patient switch to night ,patient again admitted for blood sampling. Blood withdraw hourly for 24 hours. Outcome was measured in form of TSH, free T4,T4, reverse T3,serum levels of TBG and albumin concentration.

A significant decrease was present in TSH and thyroid hormone level after switching from morning to bed time. 24 hour average value (mean±SD, morning vs bed time ingestion).TSH 5.1±0.9 vs 1.2±0.3($p<0.01$),free T4 16.7±1.0 vs 19.3±0.7($p<0.01$),T3 1.5±0.05 vs 1.6±0.1(p,0.01). There is no significant changes in T4, rT3, albumin, TBG serum level normal in T3/rT3 ratio. The relative amplitude and time of nocturnal TSH surge remain intact. High level thyroid hormone and low TSH concentration was present in primary hypothyroidism taking bed time levothyroxine Circadian rhythm of TSH stay intact

Effect of levothyroxine administration time on serum TSH in elderly patients Retrospective study conducted by **Elliott DP et al**[8]

In common clinical practice levothyroxine was taken morning before breakfast due to food and other medication interferes the absorption of levothyroxine . Objective was to find out effect of changing the levothyroxine from morning to midnight. Done in 187 bedded skilled nursing facility. 15 patients of nursing home facility receiving levothyroxine was included mean age of 84 years , inclusion criteria was patients should have atleast two TSH value (1)before the change of levothyroxine from morning to midnight (2) after the change of levothyroxine from morning to midnight.

There was decrease in TSH value (0.286±1.722) after changing the levothyroxine taking midnight . that was not statistically significant (p=0.532). Levothyroxine could be routinely administered after taking breakfast

STUDY JUSTIFICATION

There had been many studies in adults to assess the effectiveness of bedtime levothyroxine intake when compared to morning levothyroxine administration. To the best of our knowledge, no such type of study has been designed in children. Many parents with hypothyroid children found it inconvenient to administer the drug on an empty stomach in the morning because of

- Busy schedule of parents.
- Difficulty in cajoling the school going children in the morning.
- Many parents are not willing to administer the drugs for the fear that the child may skip the breakfast

If proved that evening dose of levothyroxine is equally efficacious as morning dose in children, it will be useful for parents of hypothyroid children.

OBJECTIVES-

Primary objective

To assess effectiveness of bedtime Levothyroxine administration as compared to morning Levothyroxine administration.

Secondary objective

To assess changes in other biochemical parameters like creatinine and lipid levels, in anthropometry indices like body mass index, in vital signs like heart rate, blood pressure when compared to early morning empty stomach regimen.

MATERIALS AND METHODS

STUDY DESIGN

Open label randomized control study

STUDY SETTING

Endocrinology OPD of Institute of Child Health and Hospital for Children.

STUDY PERIOD

September 2015 to August 2016.

TIMELINE

DATA COLLECTION - September 2015 to August 2016

DATA ANALYSIS AND MANUSCRIPT PREPARATION - August 2016

SUBMISSION OF REPORT – September 2016

STUDY POPULATION

Children on follow up in endocrinology OPD who were diagnosed to have hypothyroidism, on levothyroxine supplementation and in euthyroid state at the start of study after meeting inclusion and exclusion criteria.

SAMPLE SIZE

For calculation of sample size, results from the pilot study conducted by Bolk et al was used where it was found that to get a significant difference in TSH of 1.5 mIU/L in both the groups at the end of study with a power of 80%, 77 subjects should be enrolled in each group hence the same was followed.

INCLUSION CRITERIA

All children above 3 years of age who have been diagnosed to have hypothyroidism and on treatment, with T3,T4 and TSH within normal range.

EXCLUSION CRITERIA

Children with GIT disorder, malabsorption syndrome or taking medication known to interfere with uptake of levothyroxine.

CASE DEFINITION

All biochemically confirmed cases of hypothyroidism under treatment.

ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the Institutional Review Board. Informed written consent was obtained from the parents of the study subjects. Strict confidentiality of data was maintained throughout the study.

STUDY MANOUVERE

1. Out of 250 children who are on regular follow up, 154 children satisfying inclusion and exclusion criteria were recruited into the study.
2. Informed written consent was obtained from the parents of study subjects.
3. Children were randomly allocated into two groups. One group received levothyroxine in early morning (1hr before food) and another group received levothyroxine in bedtime (2hrs after food) upto 3 months.
4. Recommended levothyroxine dosage:

AGE	LEVOTHYROXINE DOSAGE (mcg/kg)
0-3 mths	10-15
3-6 mths	8-10
6-12 mths	6-8
1-3 yrs	4-6
3-10 yrs	3-4
10-15yrs	2-4

The above dosage was used to treat hypothyroidism. Before the start of the study dose of levothyroxine was adjusted to achieve the euthyroid state but after starting the study, same dose of levothyroxine was maintained throughout.

5. Though it was difficult to change over the patient from morning to bedtime regimen because patients were already adapted to particular regimen and this change of timing of levothyroxine may lead to poor compliance of levothyroxine intake, this problem was overcome with daily maintenance of diary of recording the time of levothyroxine and food intake, regular clinic follow up and through phone call.
6. The baseline demographic characteristics and clinical characteristics were obtained from all the children at the time of start of study.
7. Age was calculated in months from the date of birth.

8. Anthropometric parameters (height, weight and BMI) were measured at baseline and 12 weeks. Vital parameters, TSH, free T4, lipid profile and renal parameters were measured at baseline, 6 weeks and 12 weeks.
9. Height was measured by making the child stand bare-footed and the heel, buttocks, shoulders and occiput touching the wall and looking straight ahead. Measurements were read directly after lowering the cursor or placing horizontally held wooden board to touch the top of the head. Accuracy to the nearest 0.2 cm. Z-score was calculated by using WHO charts for children below 5 years and IAP chart above 5 years.
10. Weight was measured with subjects wearing light cloths and no shoes using calibrated electronic scale. Accuracy to the nearest 100 grams.

    Z-score was calculated by using WHO charts for children below 5 years and IAP chart above 5 years.
11. BMI was calculated from standardized formula.

$$\frac{\text{Weight in kg}}{(\text{Height in meter})^2}$$

    Z-score was calculated using WHO charts for children below 5 years and IAP chart above 5 years
12. Heart rate was counted for one full minute in sitting position.

    Normal heart rate by age

Approximate age range	Heart rate
Newborn	100-160/min
0-5months	90-150/min
6-12months	80-140/min
1-3years	80-130/min
3-5years	80-120/min
6-10years	70-110/min
11-14years	60-105/min

13. BP was measured thrice at an interval of 1 minute using appropriate sized cuff in the right upper limb in sitting position after 5 minutes of rest. Sphygmomanometer was held at the level of heart. Mean value of second and third measurements was taken.

    Z-score was calculated for systolic and diastolic BP measurements separately. Data such as height, weight and age were taken into consideration while calculating the Z-score

14. Thyroid function tests:

    Thyroid function test was performed on early morning venous blood sample after 12 hours of fasting. TSH and free T4 levels were measured using enzyme immunoassay method.

    Normal values:

Parameters	Normal values
TSH	0.3-6.0mIU/L
Free T4	0.78-2.1mIU/L
Free T3	0.89-2.62mIU/L

15. Serum lipid profile:

Early morning fasting venous blood sample was collected for lipid profile analysis. Serum concentrations of Total cholesterol (CHOD POD method), HDL (direct assay method), Triglycerides (GPO method) were measured.

Cholesterol and Lipid distribution in children (50^{th} percentile values)

Lipid/Lipoprotein	Male			Female		
	1-4 years	5-9 years	10-14 years	1-4 years	5-9 years	10-14 years
Total cholesterol (mg/dl)	155	153	161	156	164	159
Triglycerides (mg/dl)	56	48	58	64	57	68
High-density lipoprotein (mg/dl)	-	55	55	-	52	52

16. Renal parameters like blood urea (enzymatic GLDH method) and serum creatinine (kinetic Joffe's method) were measured.

    Normal values:

    Blood urea: 15-39 mg/dl

    Serum creatinine: 0-4 yrs: 0.03-0.5mg/dl, 7-10yrs: 0.22-0.59mg/dl, 10-14yrs:0.31-0.88mg/dl

STATISTICAL ANALYSIS

All the descriptive statistics, frequency histograms and bar charts were created using Gnumeric spreadsheet (version: 1.12.28), a light weight spread sheet developed by Gnome open source project.

All parametric and non parametric tests and tests for categorical data were done in R programming language (R version 3.2.3 (2015-12-10) – "Wooden Christmas-Tree" Copyright © 2015 The R Foundation for statistical computing).

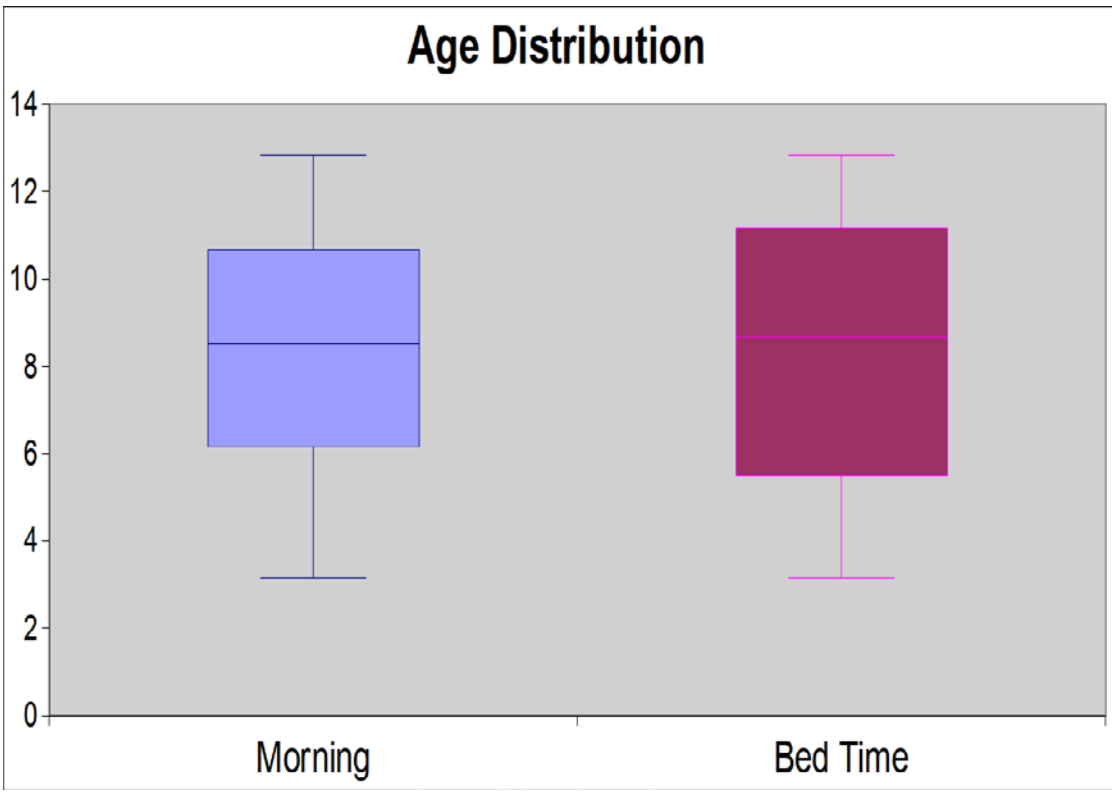
The computing platform was x86_64-Arch-Linux-gnu (64-bit).

ETHICAL CONSIDERATIONS

The study was commenced after the ethical committee clearance. Informed consent was obtained from parent. Strict confidentiality was maintained while analysing and presenting the data.

RESULTS

AGE & SEX DISTRIBUTION



The mean age for morning group is 8.32

The mean age for bedtime group is 8.44

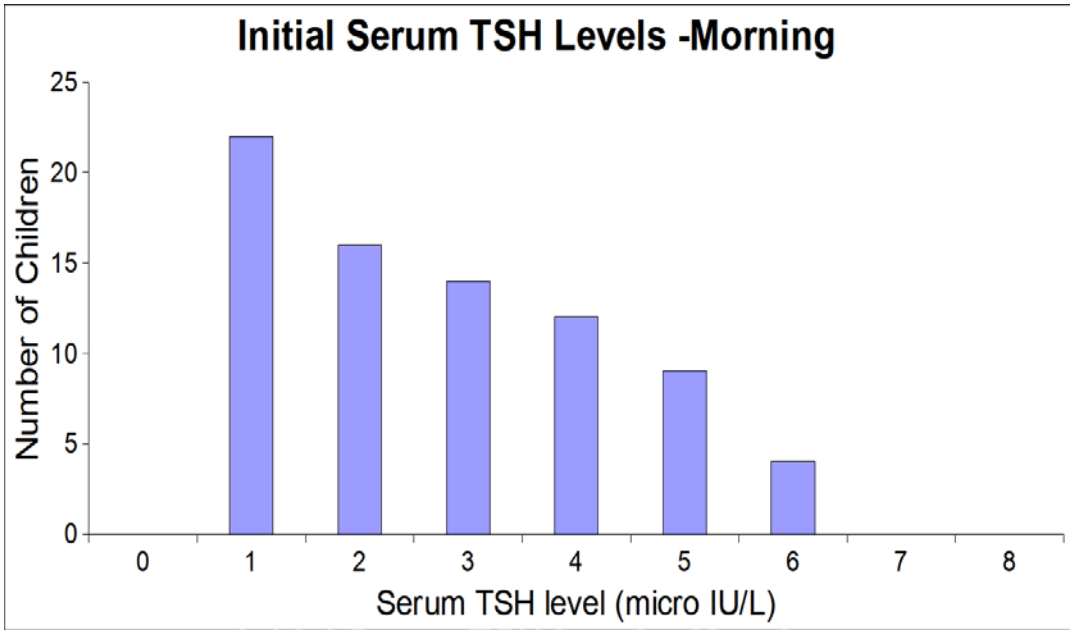
The difference in the mean age between these group is statistically not significant (P=0.8)

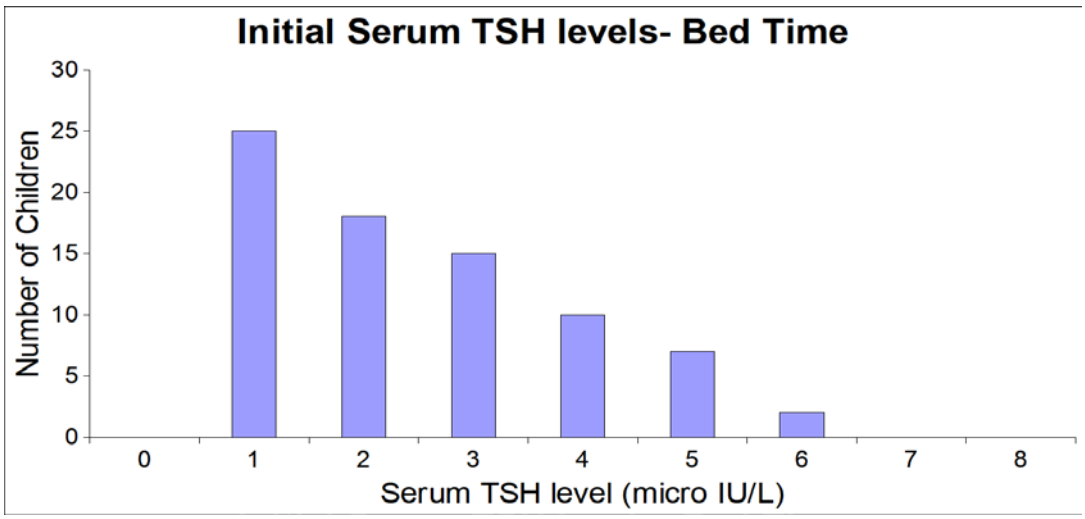
POPULATION	MALE	FEMALE
MORNING	26	51
BEDTIME	25	52

Two sample test for equality of proportion with continuity correction

P = 1

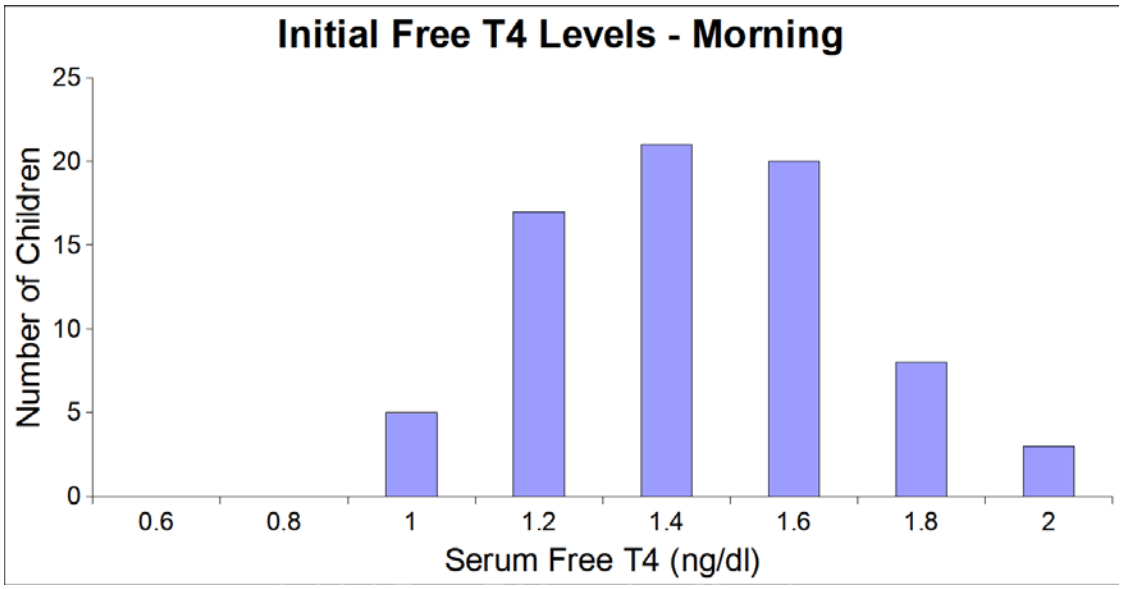
The difference in sex distribution among these two group statistically not significant

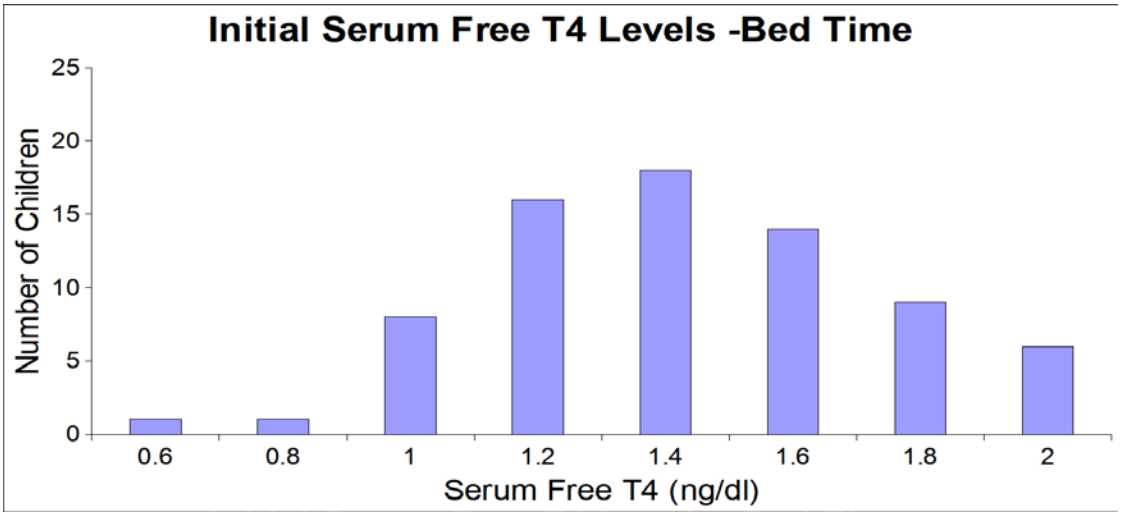




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	2.17 ± 0.36	0.24	0.99	0.32
BED TIME	1.93 ± 0.34			

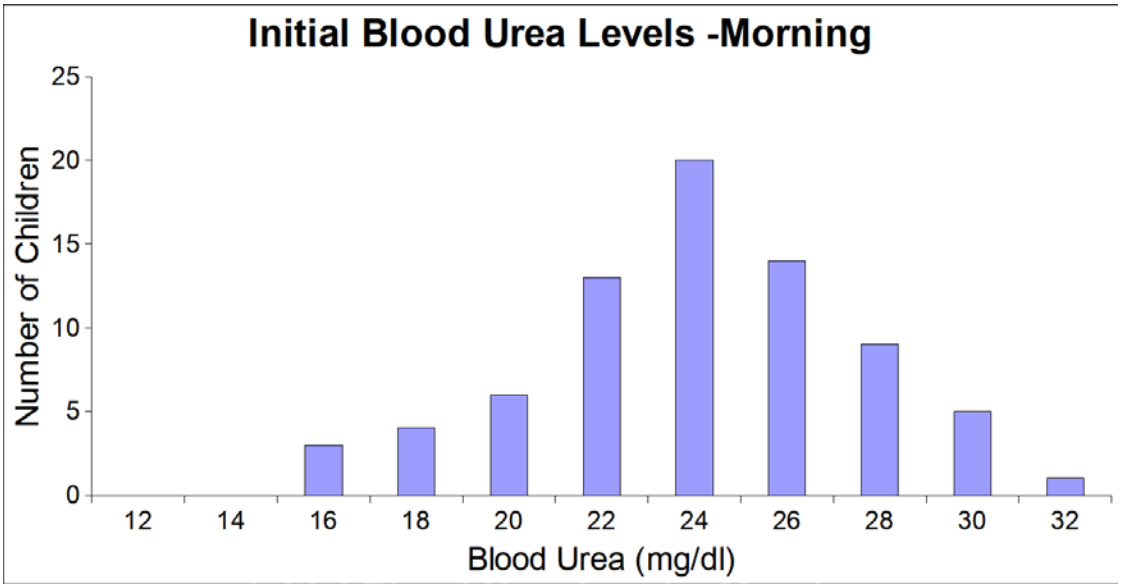
The initial mean TSH value of morning group (2.17) is higher than bedtime group (1.93). The difference in mean TSH levels of two group (0.24) is statistically not significant (p = 0.32).

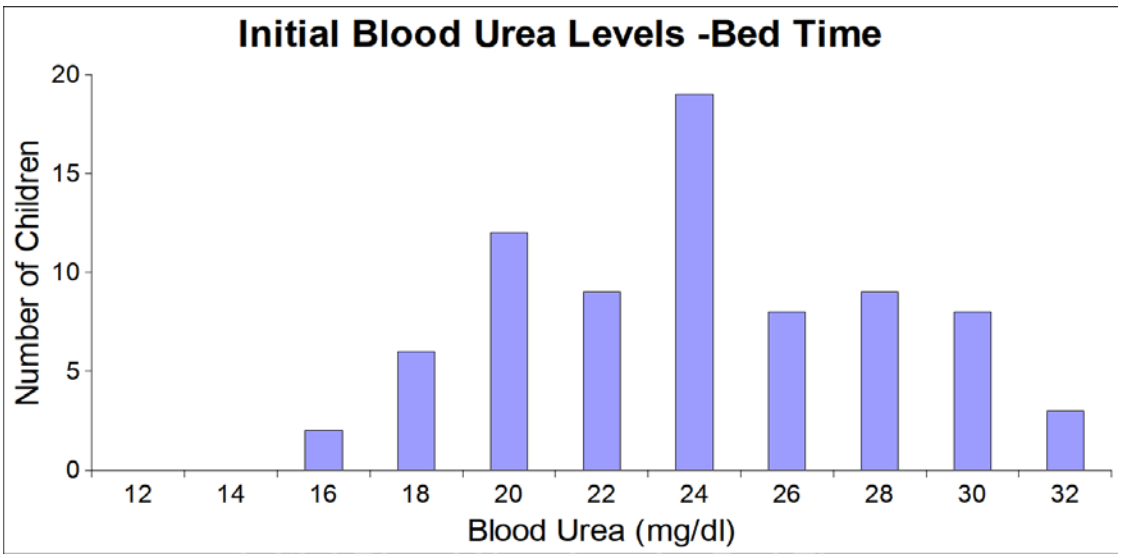




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	1.39 ± 0.66	0.01	-0.27	0.79
BED TIME	1.40 ± 0.094			

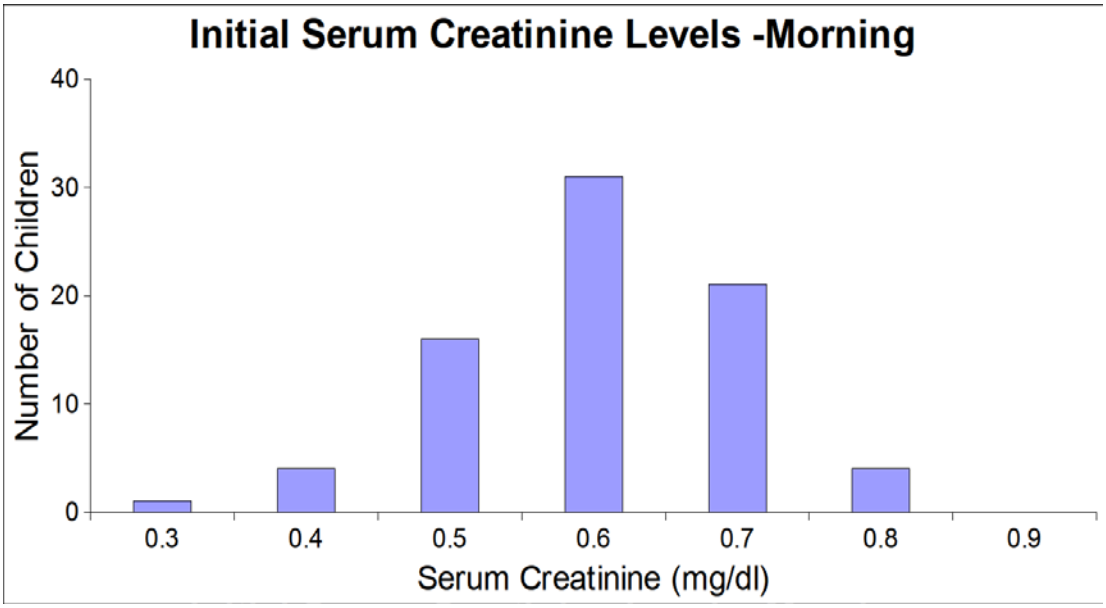
The initial mean free T4 value of bedtime group (1.40) is higher than morning group (1.39). The difference in initial mean free T4 levels of two group (0.01) is statistically not significant (p=0.79).

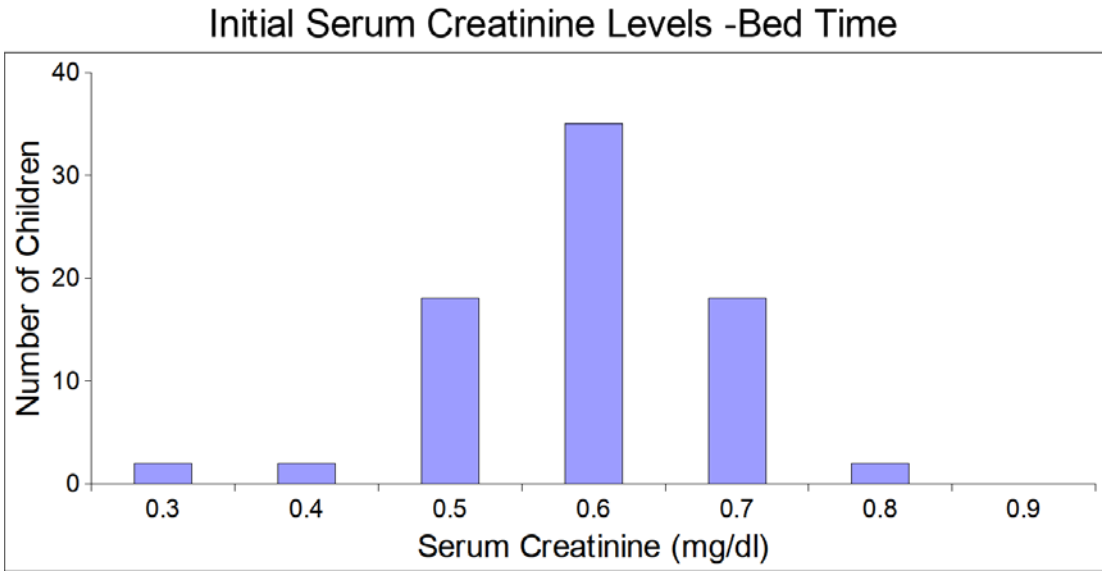




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	23.79 ± 0.87	0.090	0.14	0.88
BED TIME	23.70 ± 0.94			

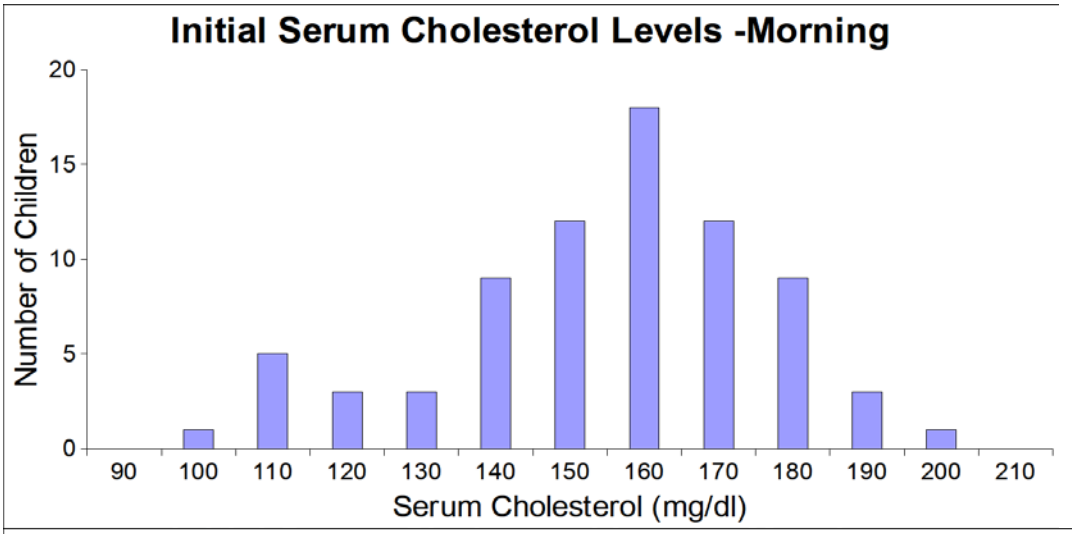
The initial mean blood urea value of morning group (23.79) is higher than bedtime group (23.70). The difference in initial mean blood urea levels of two group is statistically not significant (p=0.88).

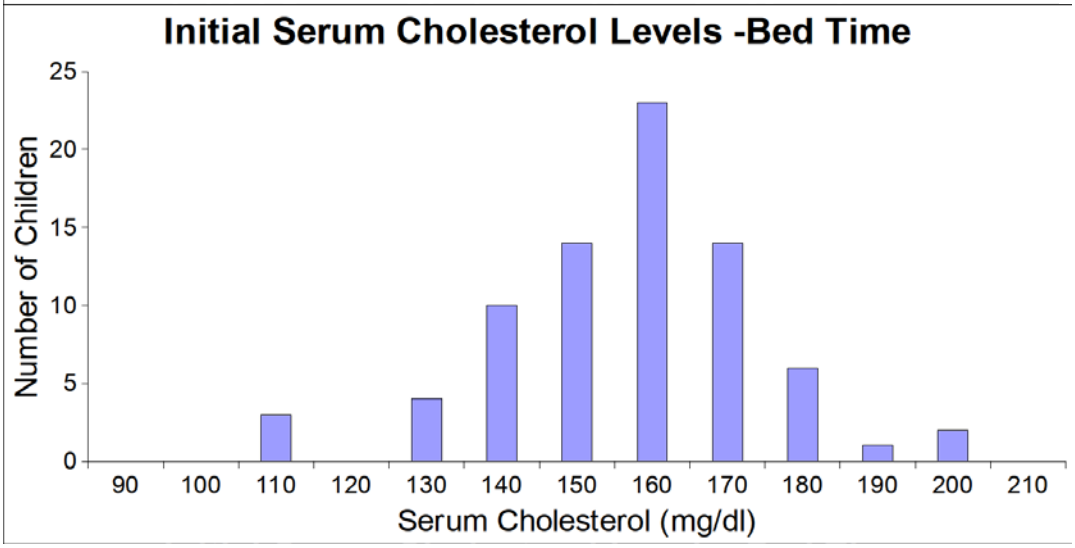




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.60 ± 0.02	0.01	0.65	0.51
BED TIME	0.59 ± 0.02			

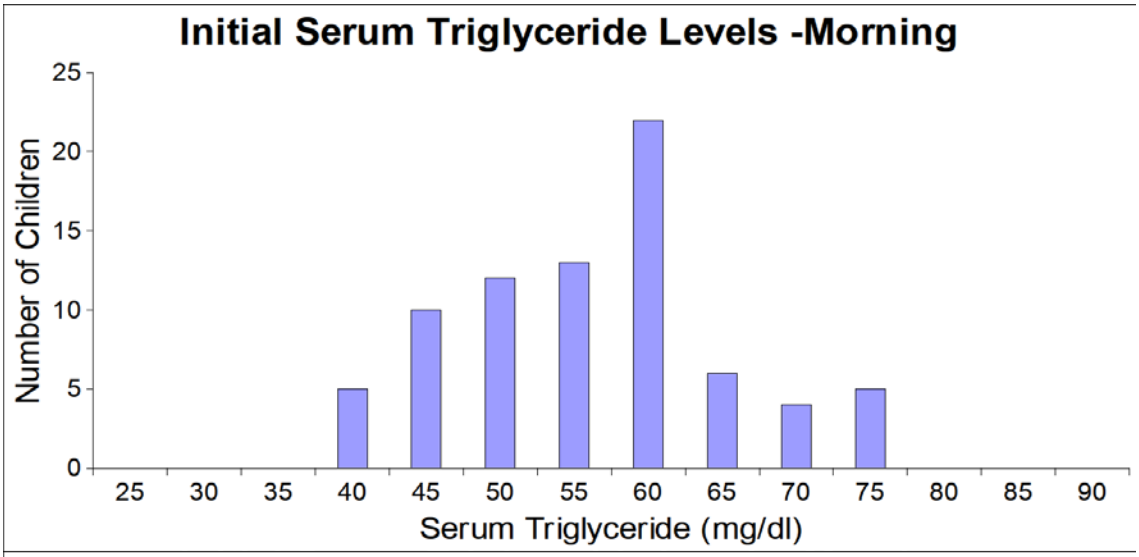
The initial mean serum creatinine value of morning group (0.60) is higher than bedtime group (0.59). The difference in initial mean serum creatinine levels of two group (0.01) is statistically not significant (p=0.51).

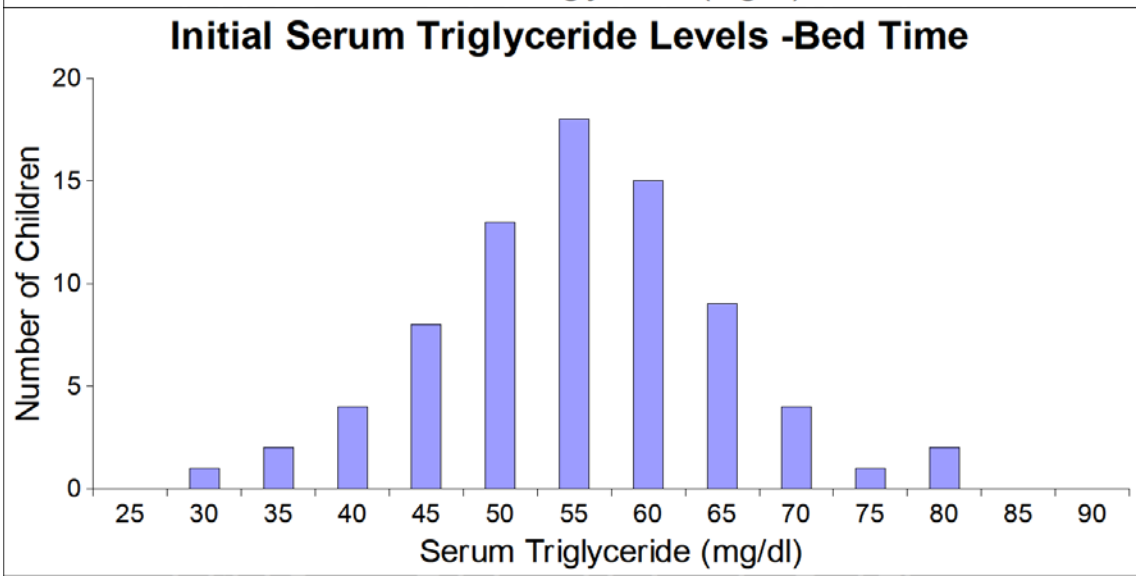




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	151.57 ± 5.86	-0.56	-0.16	0.88
BED TIME	152.13 ± 4.14			

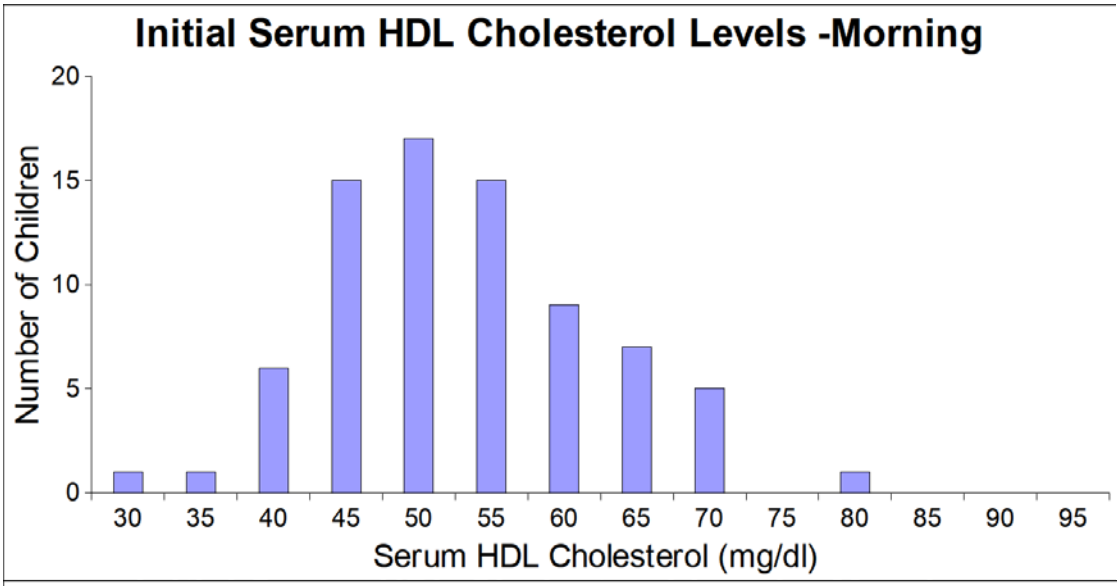
The initial mean serum cholesterol value of bedtime group (152.13) is higher than morning group (151.57). The difference in initial mean serum cholesterol levels of two group (-0.56) is statistically not significant (p=0.88).

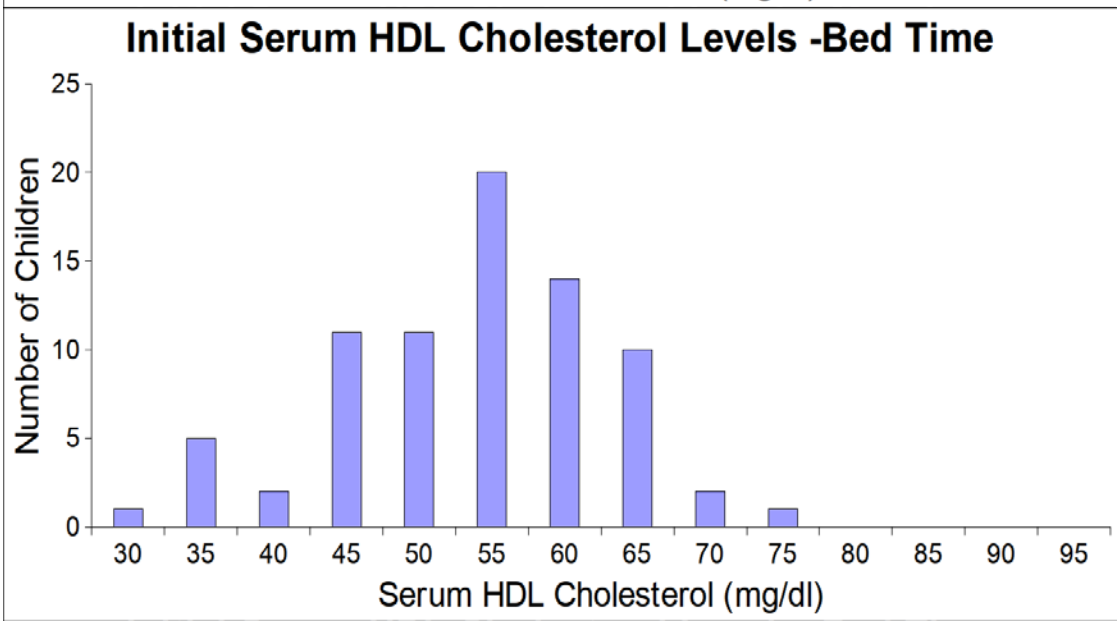




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	54.29 ± 2.02	0.82	0.55	0.58
BED TIME	53.47 ± 2.16			

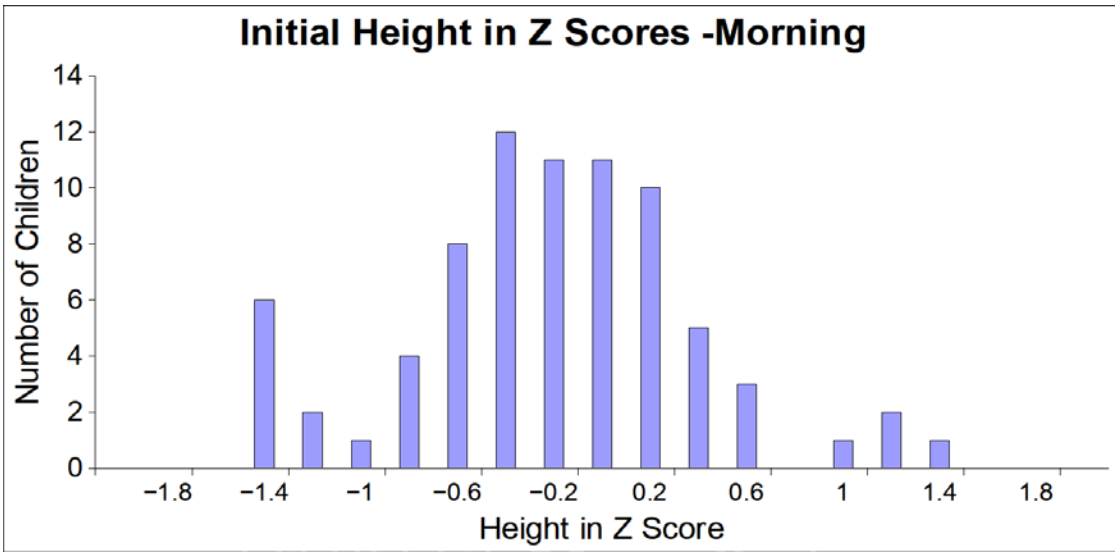
The initial mean serum triglyceride value of morning group (54.29) is higher than bedtime group (53.47). The difference in initial mean serum trigylceride levels of two group (0.82) is statistically not significant (p=0.58).

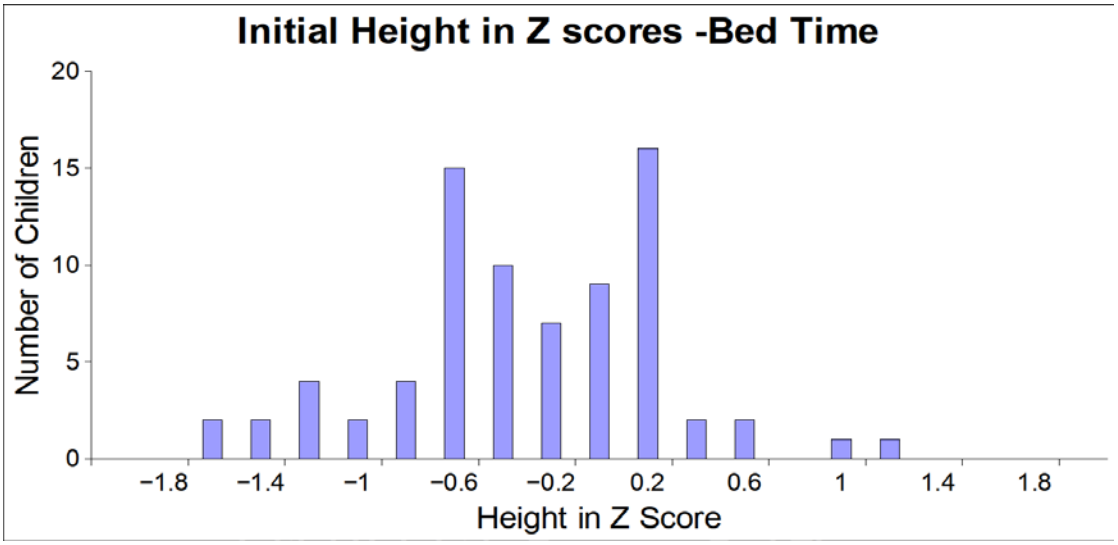




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	50.90 ± 2.12	-0.89	-0.62	0.54
BED TIME	51.79 ± 2.0			

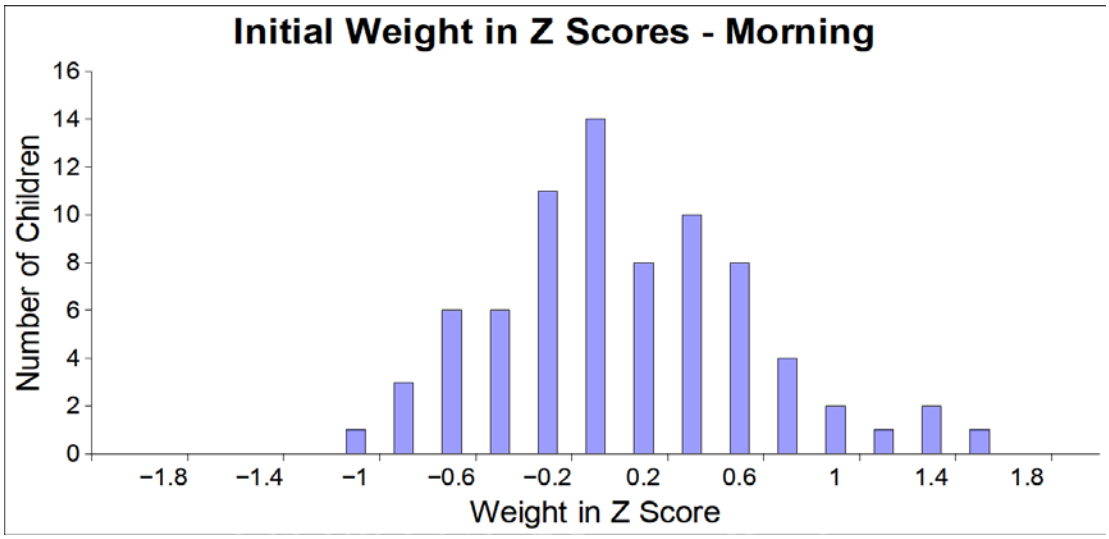
The initial mean serum HDL cholesterol value of bedtime group (51.79) is higher than morning group (50.90). The difference in initial mean serum HDL cholesterol levels of two group (-0.89) is statistically not significant (p=0.54).

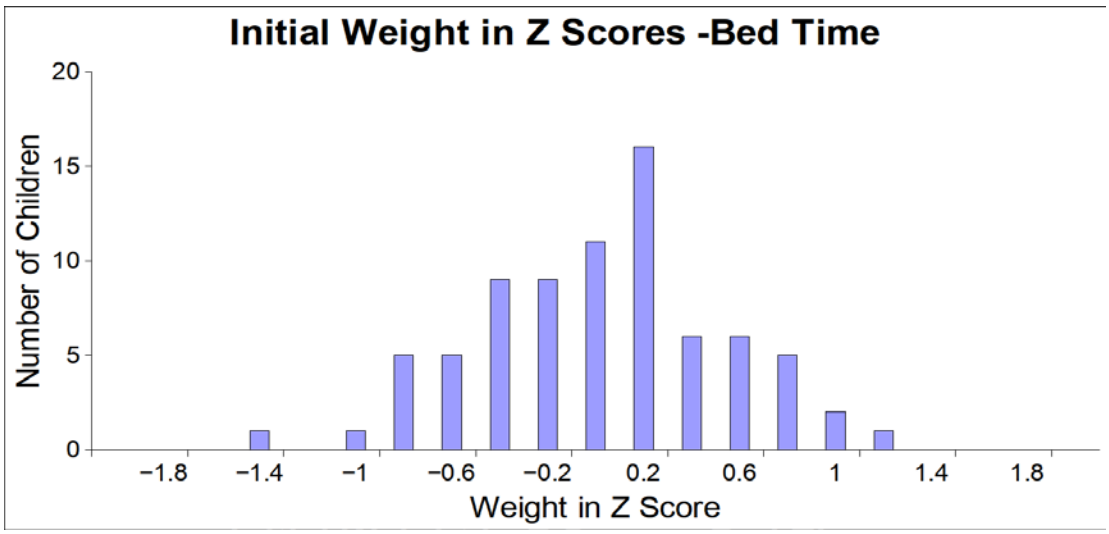




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.30 ± 0.13	0.1	1.08	0.28
BED TIME	-0.40 ± 0.12			

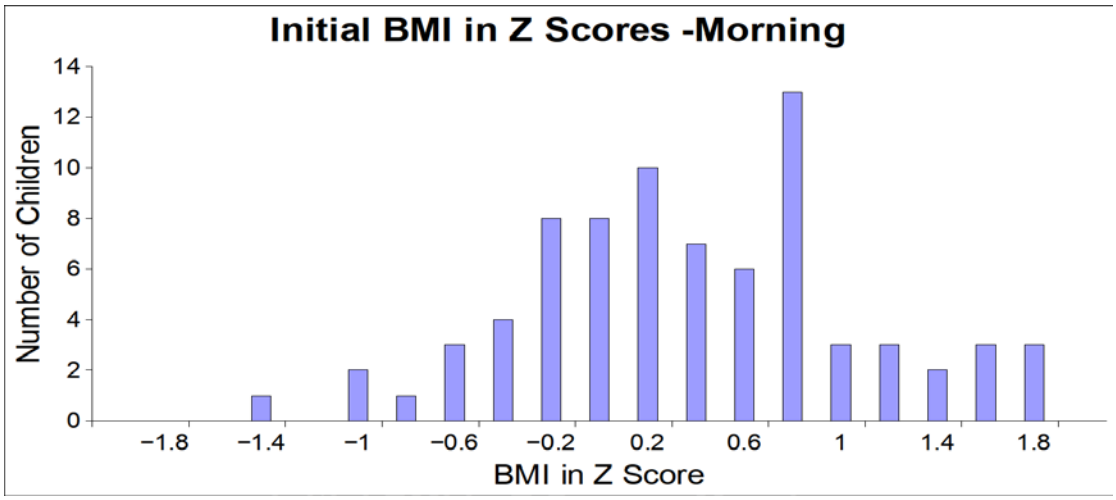
The initial mean height in Z score of morning group value(-0.30) is higher than bedtime group (-0.40). The difference in initial mean height in Z score of two group(0.1) is statistically not significant (p=0.28).

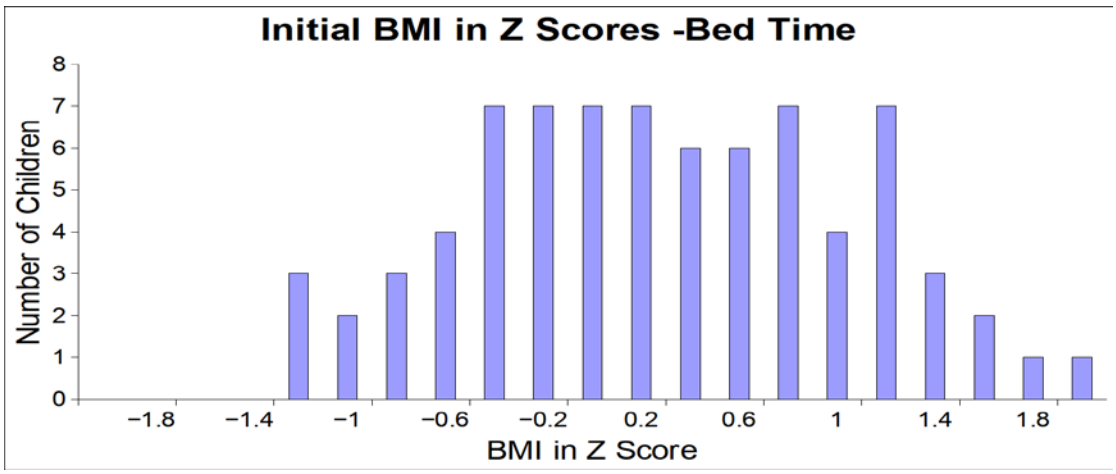




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.03 ±0.12	0.10	1.20	0.23
BED TIME	-0.07 ±0.12			

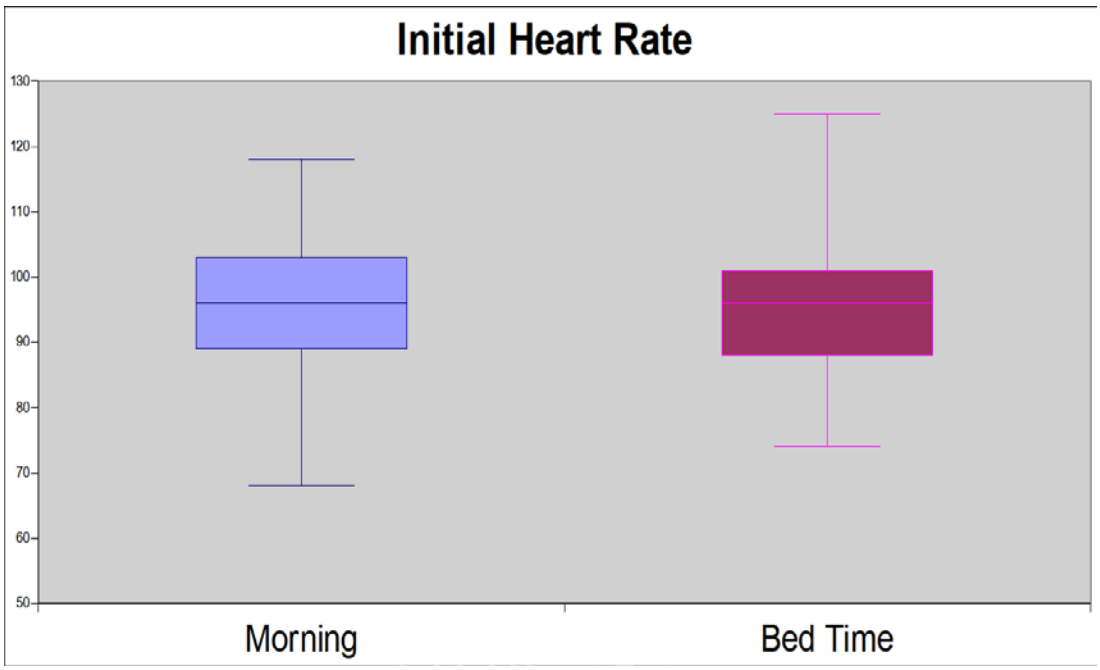
The initial mean weight in Z score value of morning group (-0.03) is higher than bedtime group (-0.07). The difference in initial mean weight in Z score value of two group(0.10) is statistically not significant (p=0.23).





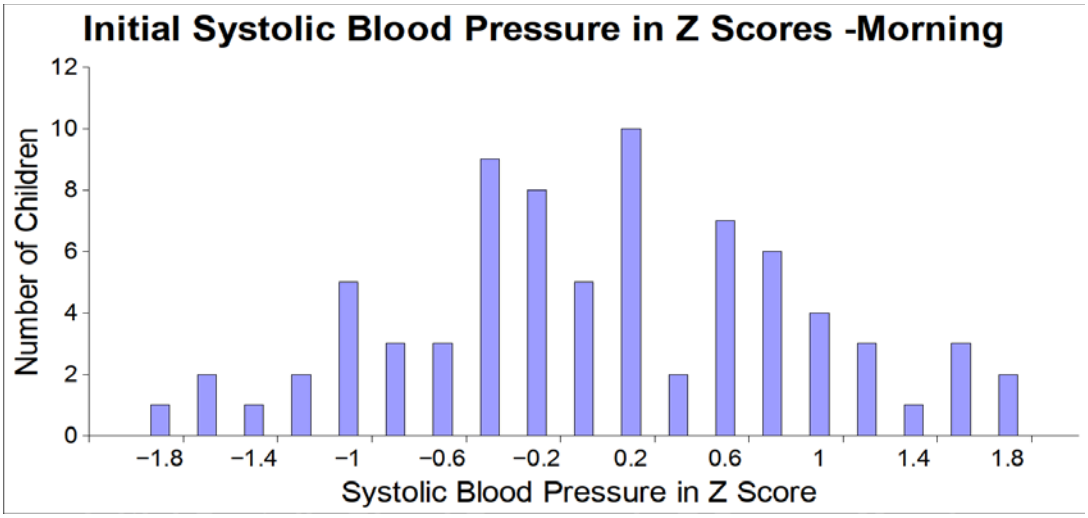
POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.28 ±0.16	0.09	0.82	0.41
BED TIME	0.19 ±0.17			

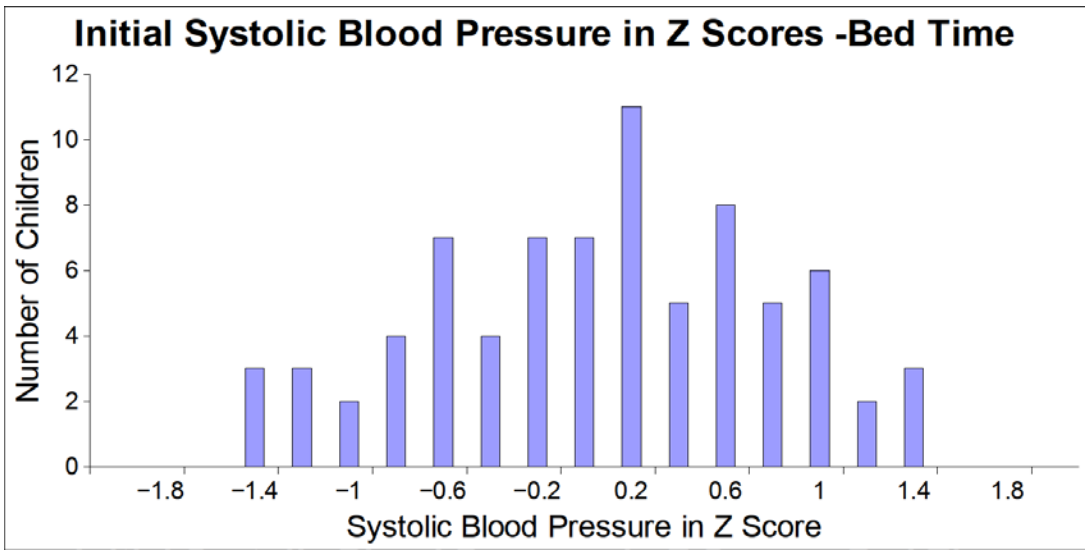
The initial mean BMI in Z score value of morning group (0.28) is higher than bedtime group (0.19). The difference in initial mean BMI in Z score value of two group(0.09) is statistically not significant (p=0.41).



POPULATION	MINIMUM	1ST QUARTILE	MEDIAN	MEAN	3RD QUARTILE	MAXIMUM
MORNING	68.00	89.00	96.00	95.29	103.00	118.00
BEDTIME	74.00	88.00	96.00	95.71	101.00	125.00

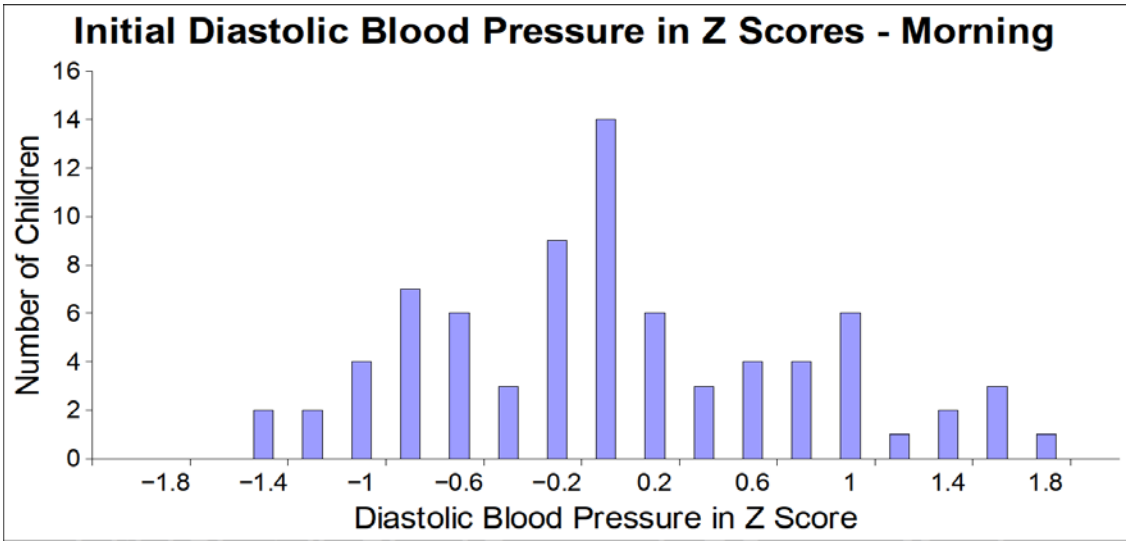
In morning group Heart rate ranged from 68 to 118 . In bedtime group Heart rate ranged from 74 to 125. The difference in the mean Heart rate of these two group is very minimal.

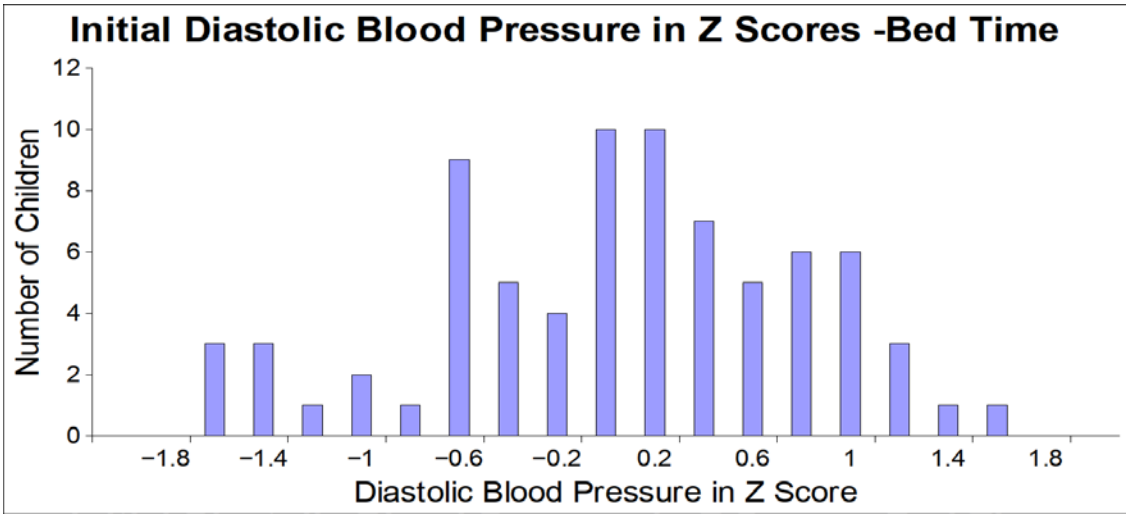




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.02 ±0.19	0.01	0.11	0.91
BED TIME	-0.03 ±0.17			

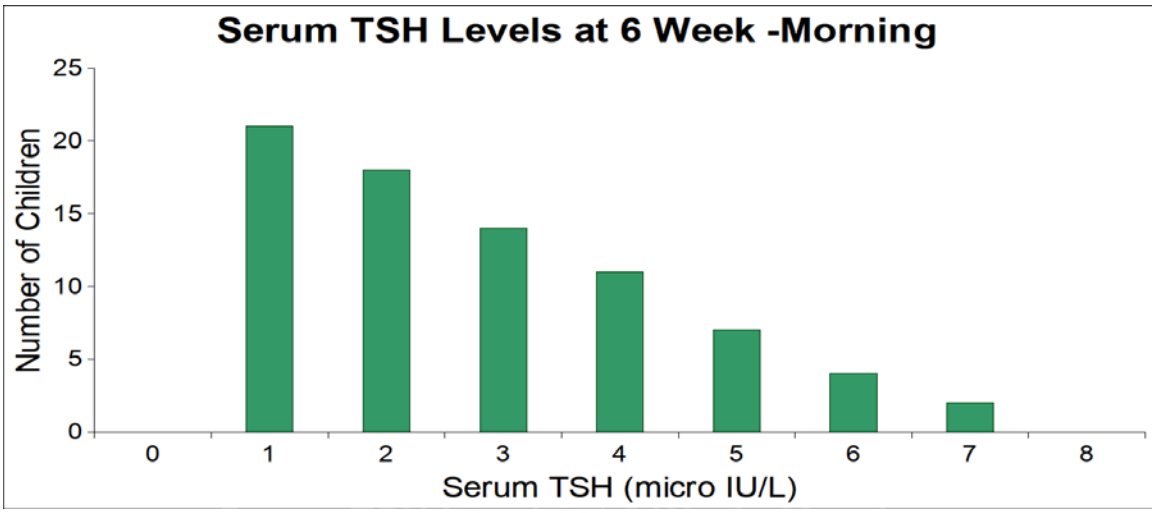
The initial mean systolic BP in Z score value of morning group (-0.02) is higher than bedtime group (-0.03). The difference in initial mean systolic BP in Z score value of two group(0.01) is statistically not significant (p=0.91).

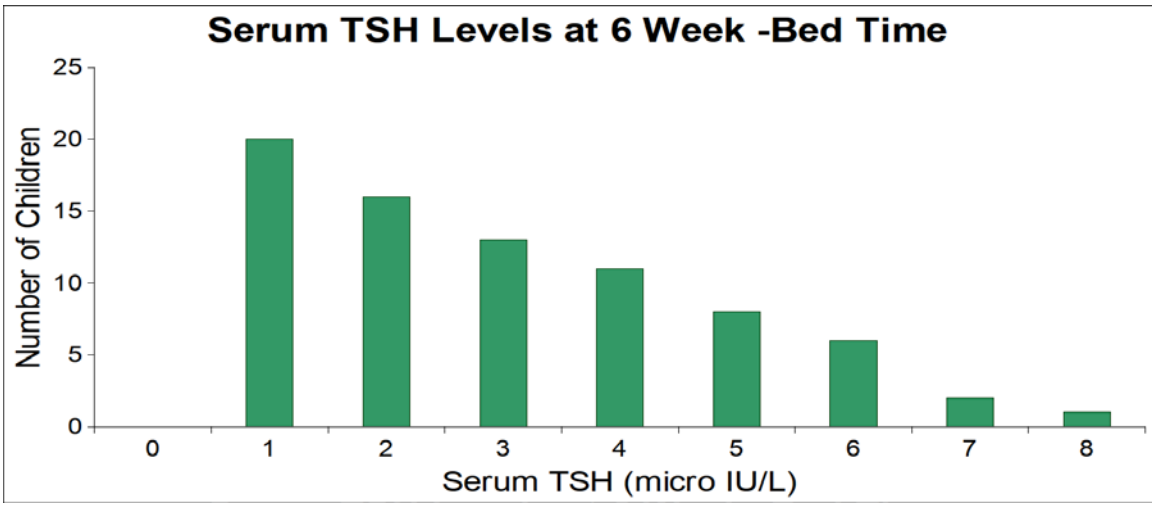




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.05 ± 0.18	-0.01	-0.09	0.92
BED TIME	-0.04 ±0.18			

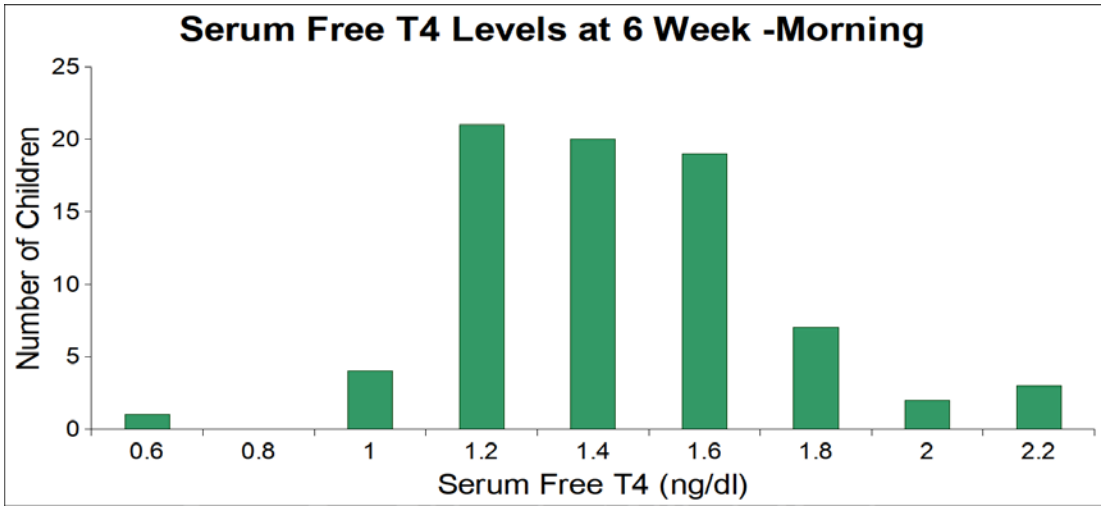
The initial mean diastolic BP in Z score value of bedtime group (-0.04) is higher than morning group (-0.05). The difference in initial mean diastolic BP in Z score value of two group(-0.01) is statistically not significant (p=0.92).

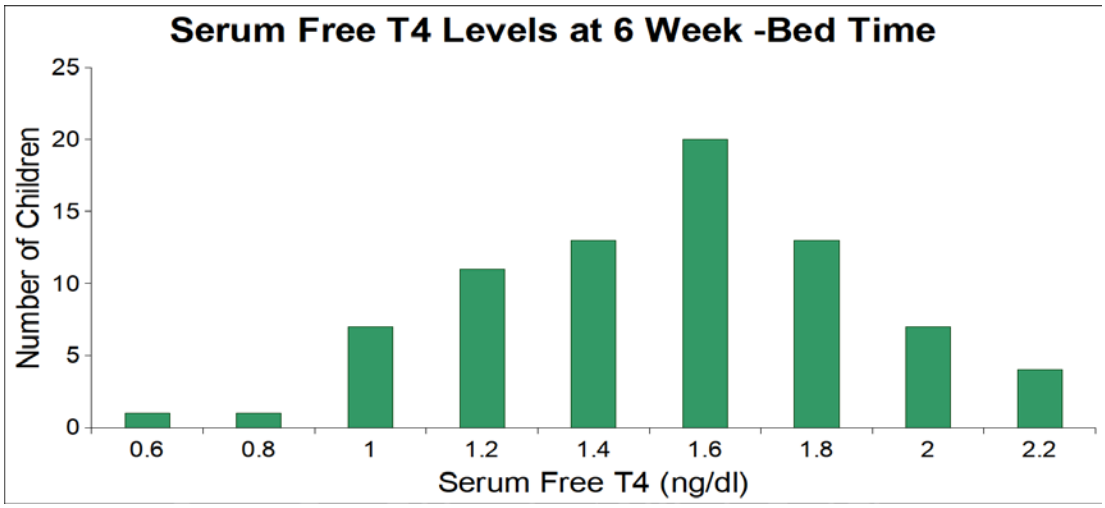




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	2.35 ±0.38	-0.07	-0.25	0.8
BED TIME	2.42 ±0.40			

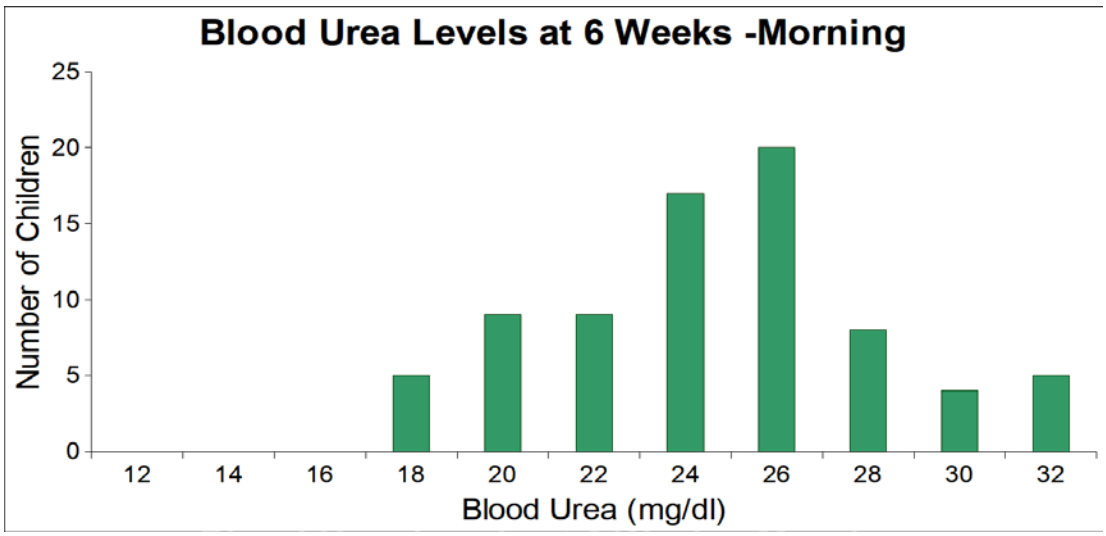
The sixth week TSH value of bedtime group (2.42) is higher than morning group (2.35). The difference in sixth week mean TSH levels of two group(-0.07) is statistically not significant (p=0.8).

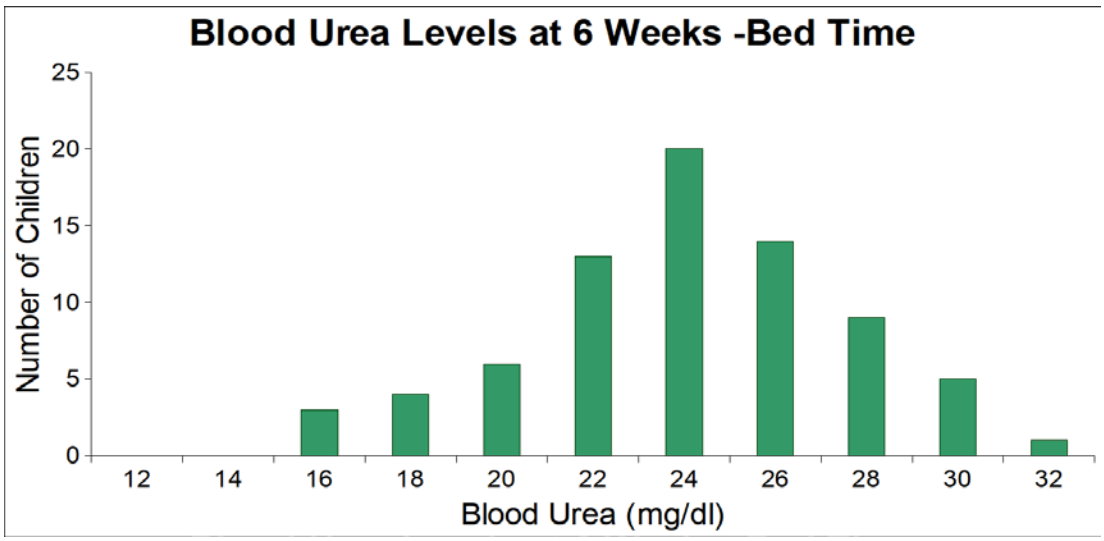




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	1.33 ±0.2	-0.12	-2.14	0.03
BED TIME	1.45 ±0.08			

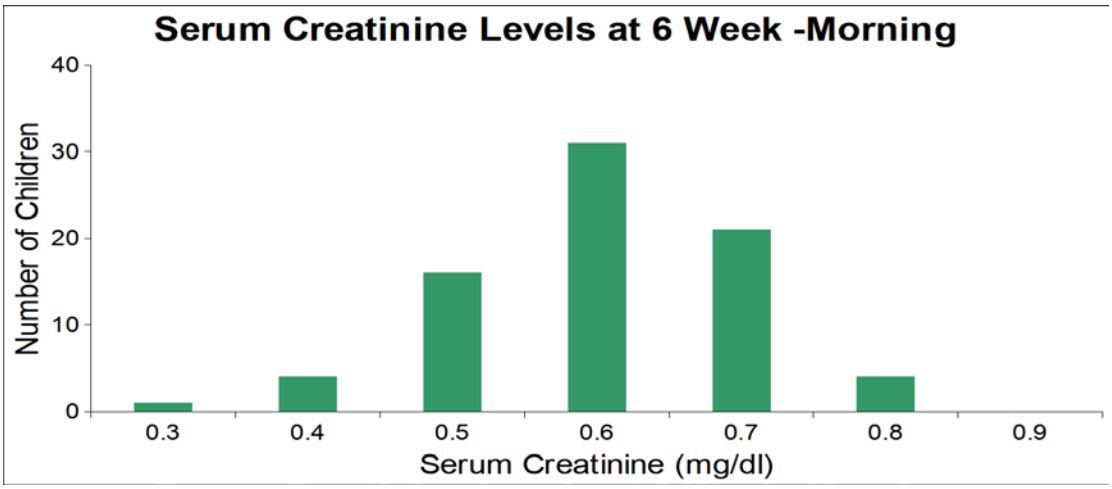
The sixth week mean free T4 levels of bedtime group (1.45) is higher than morning group (1.33). The difference in sixth week mean free T4 levels of two group(-0.12) is statistically significant (p=0.03).

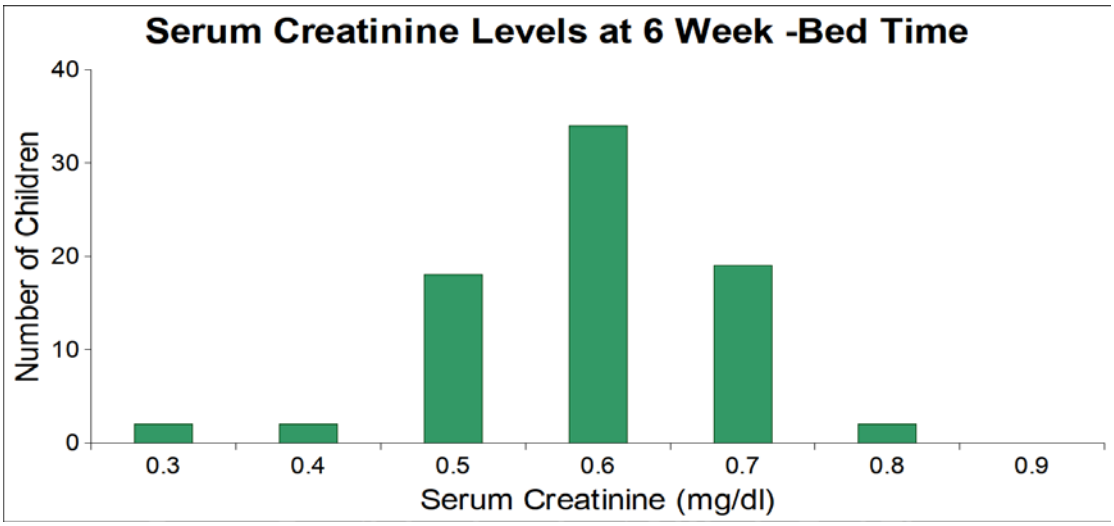




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	24.14 ±0.82	0.35	0.59	0.56
BED TIME	23.79 ±0.86			

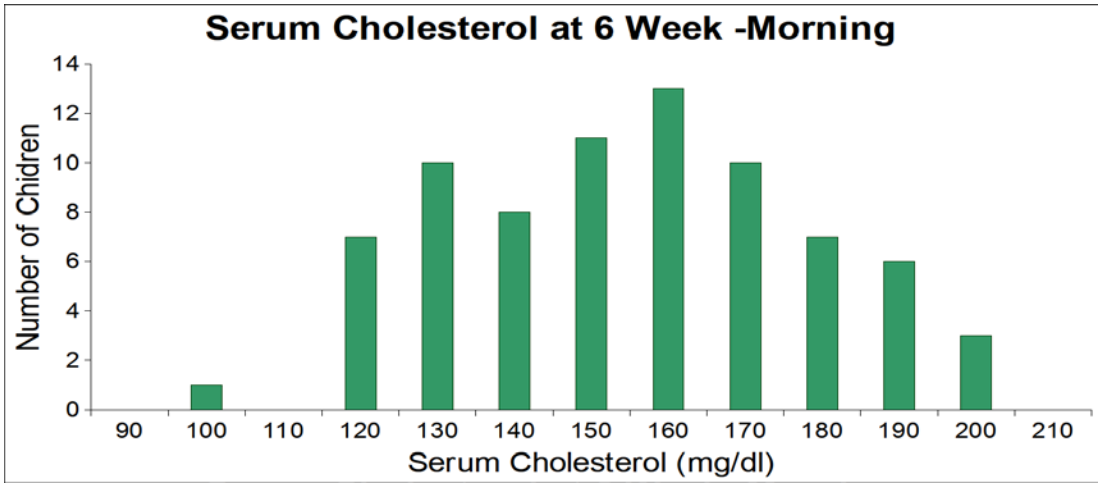
The sixth week mean blood urea levels of morning group (24.14) is higher than bedtime group (23.79). The difference in sixth week mean blood urea levels of two group(0.35) is statistically not significant (p=0.56).

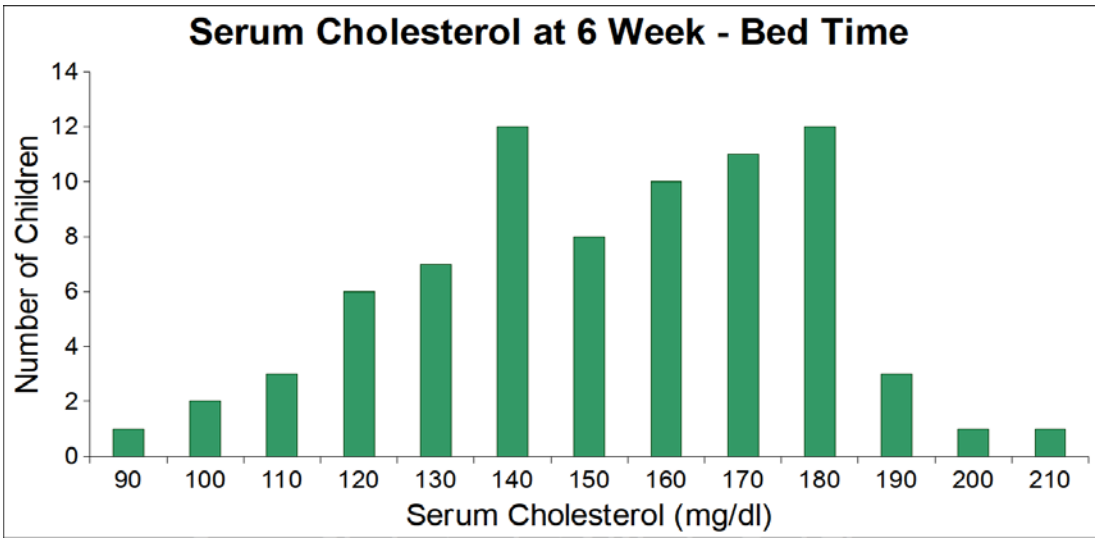




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.60 ±0.02	0.01	0.57	0.57
BED TIME	0.59 ±0.02			

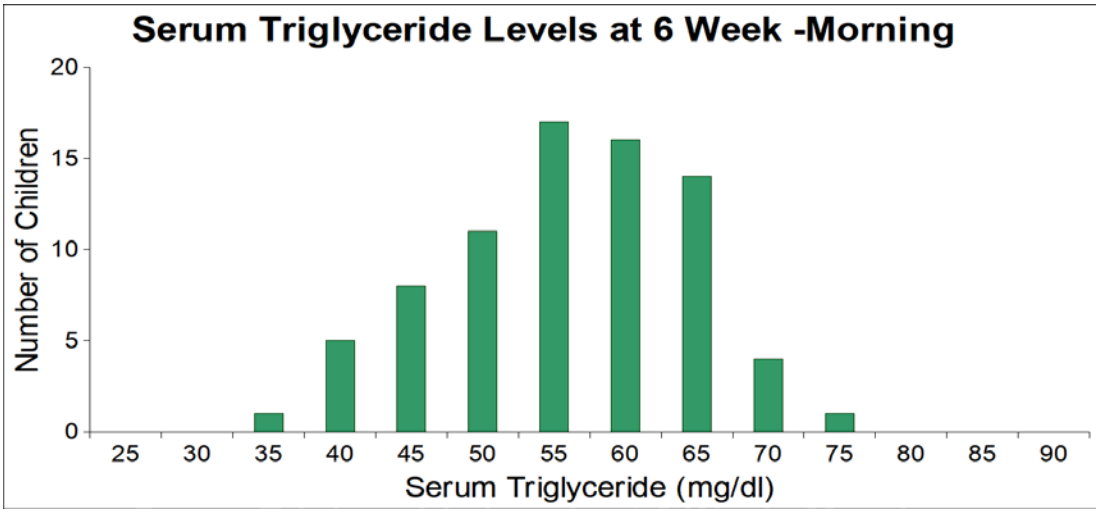
The sixth week mean serum creatinine levels of morning group (0.60) is higher than bedtime group (0.59). The difference in sixth week mean serum creatinine levels of two group(0.01) is statistically not significant (p=0.57).

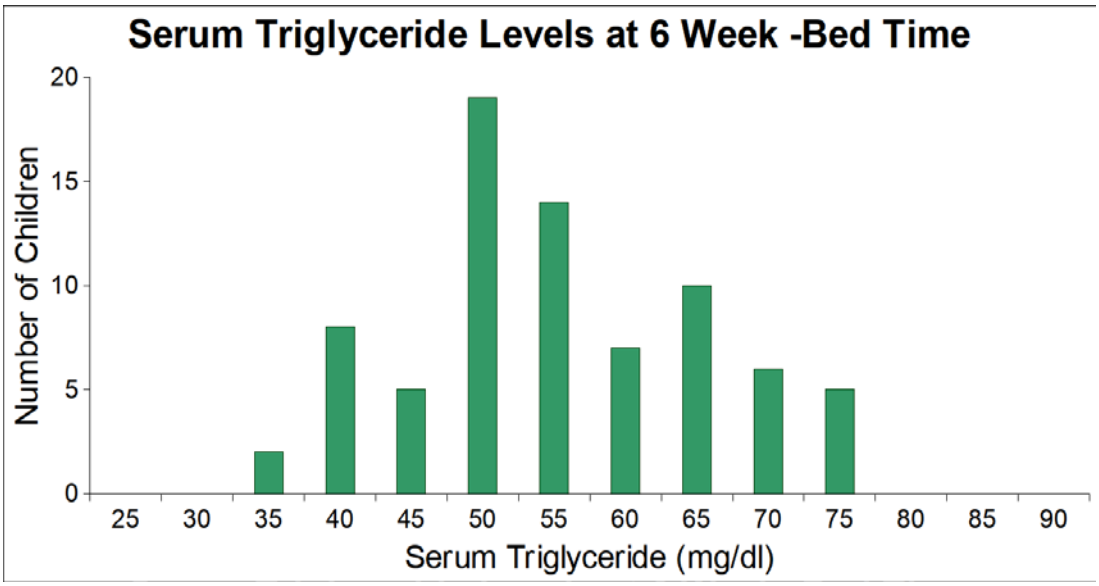




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	151 .17 ±5.6	3.46	0.85	0.39
BED TIME	147.71 ±5.82			

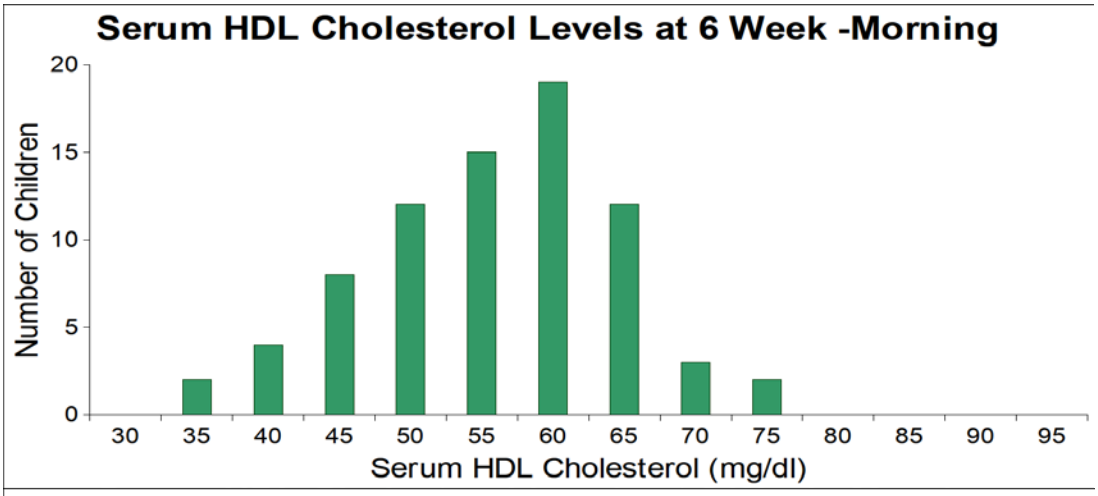
The sixth week mean serum cholestrol value of morning group (151.17) is higher than bedtime group (147.71). The difference in sixth week mean serum cholesterol value of two group(3.46) is statistically not significant (p=0.39).

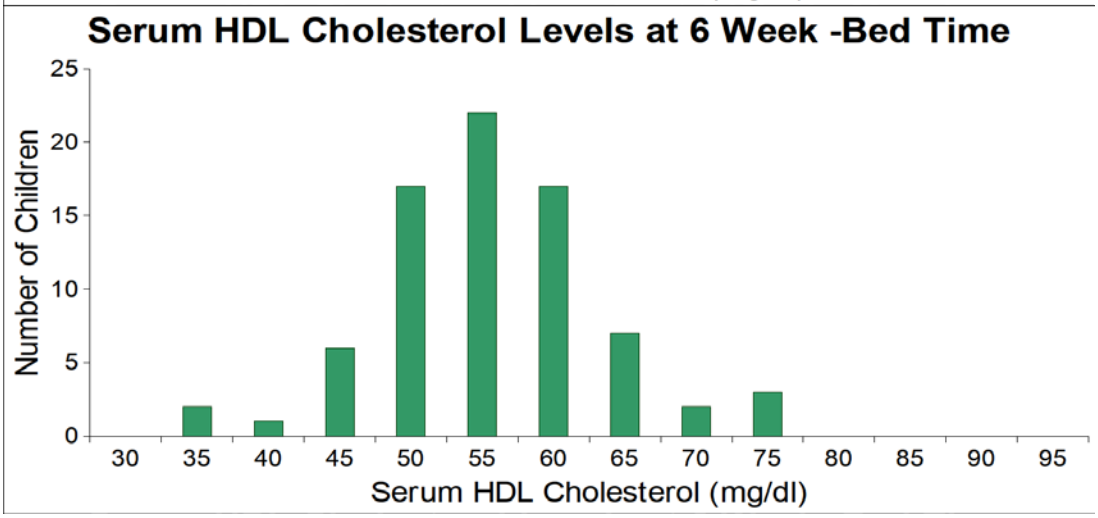




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	53.88 ±1.92	-0.12	-0.07	0.94
BED TIME	54 ±2.56			

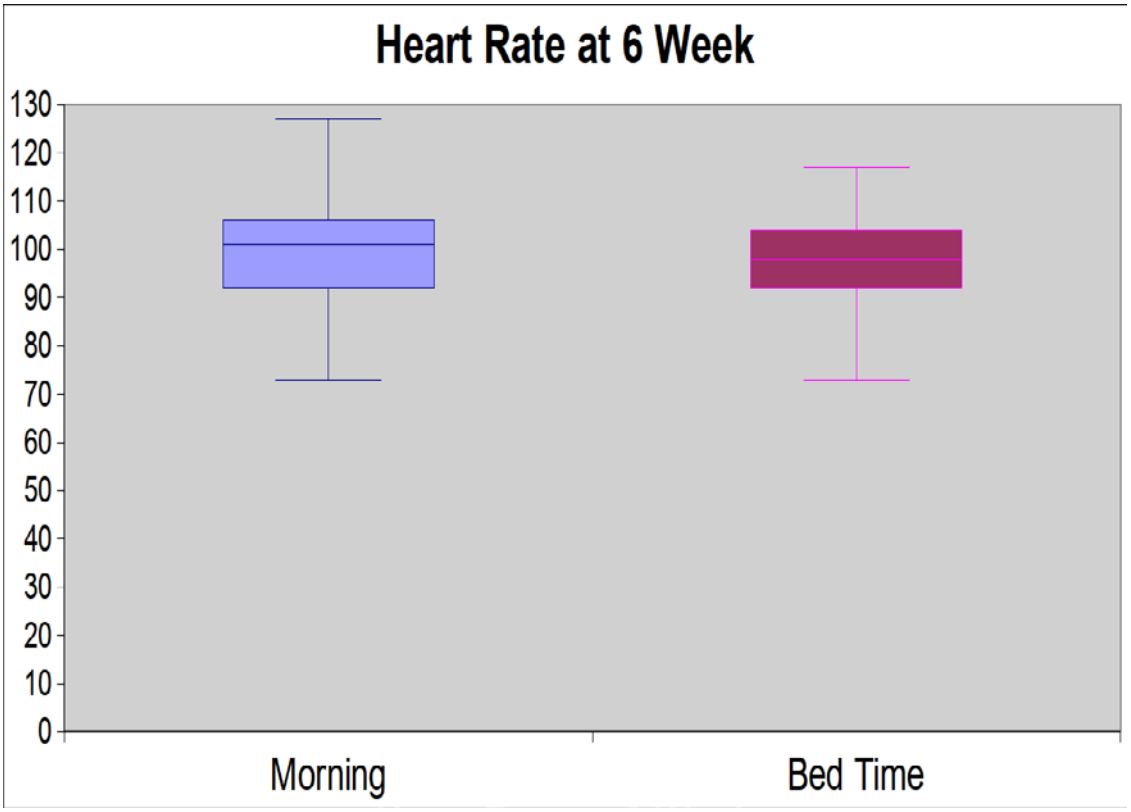
The sixth week mean serum triglyceride value of bedtime group (54) is higher than morning group (53.88). The difference in sixth week mean serum triglyceride value of two group(-0.12) is statistically not significant (p=0.94).





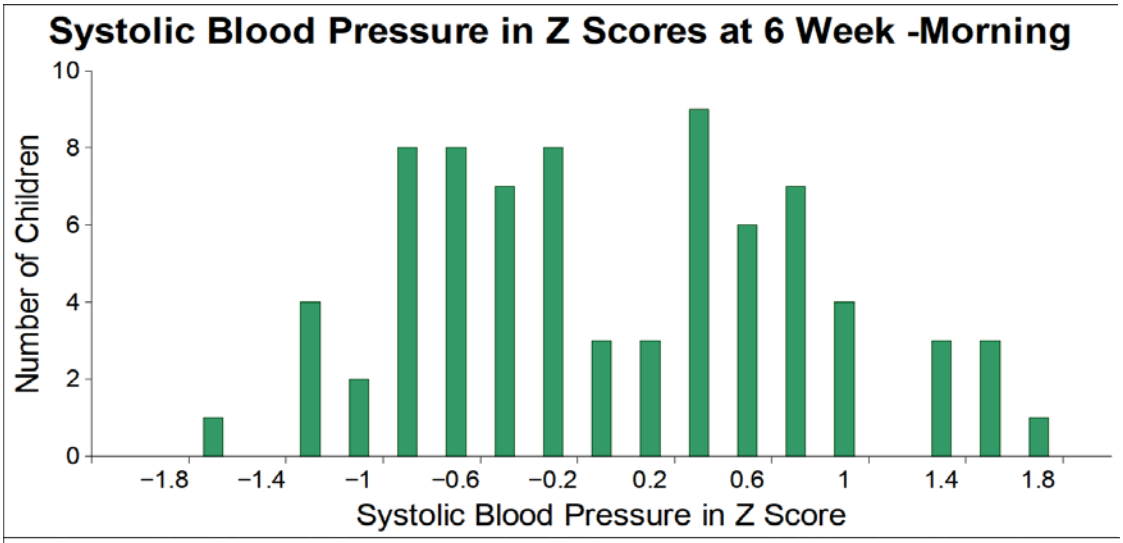
POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	53.95 ±1.98	0.38	0.28	0.78
BED TIME	53.57 ±1.8			

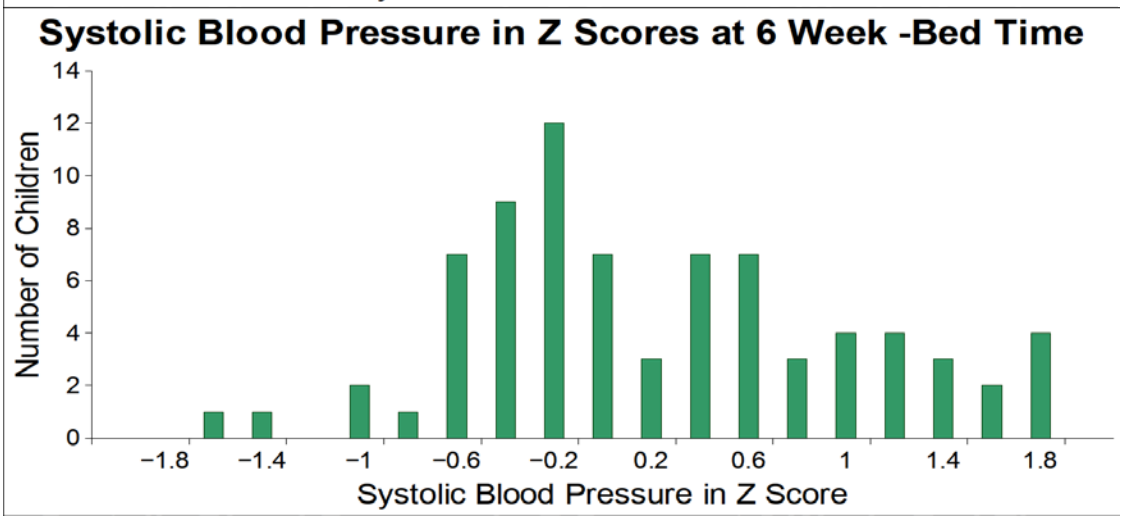
The sixth week mean serum HDL cholesterol value of morning group (53.95) is higher than bedtime group (53.57). The difference in sixth week mean serum HDL cholesterol value of two group(0.38) is statistically not significant (p=0.78).



POPULATION	MINIMUM	1ST QUARTILE	MEDIAN	MEAN	3RD QUARTILE	MAXIMUM
MORNING	73.00	92.00	101.00	99.04	106.00	127.00
BEDTIME	73.00	92.00	98.00	98.43	104.00	117.00

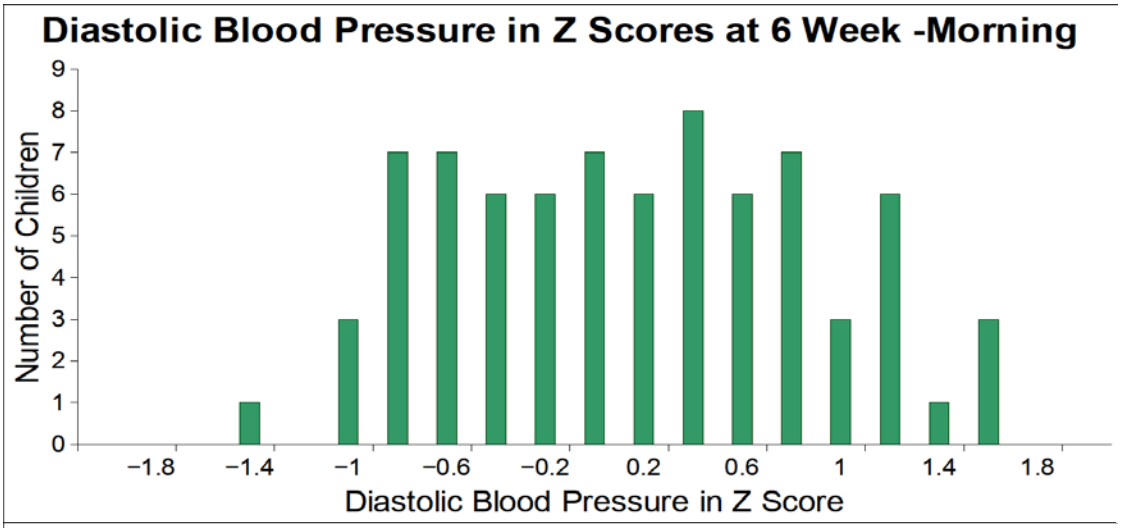
In morning group Heart rate ranged from 73 to 127 . In bedtime group Heart rate ranged from 73 to 117. The difference in the mean Heart rate of these two group is very minimal.

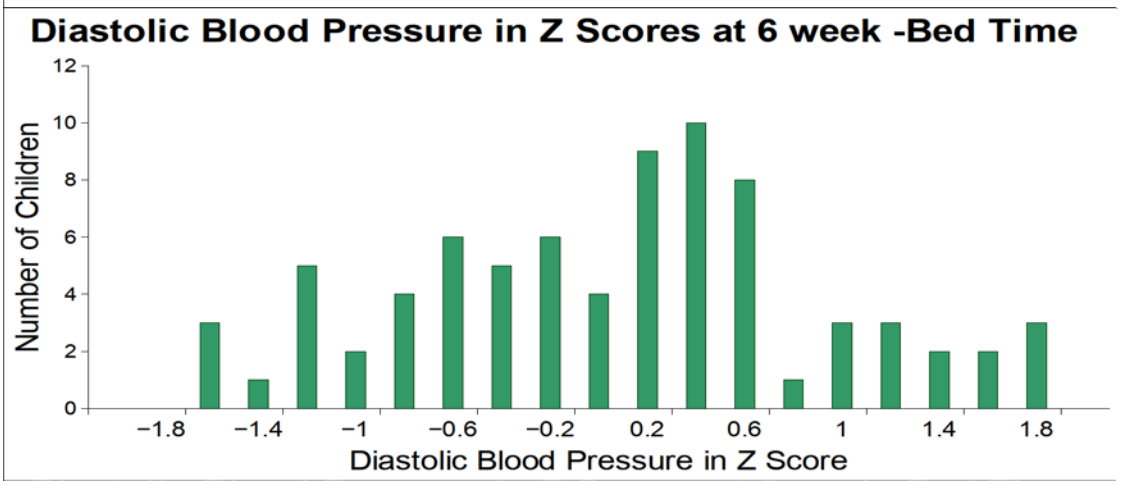




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.04±0.18	-0.18	-1.36	0.18
BED TIME	0.14±0.18			

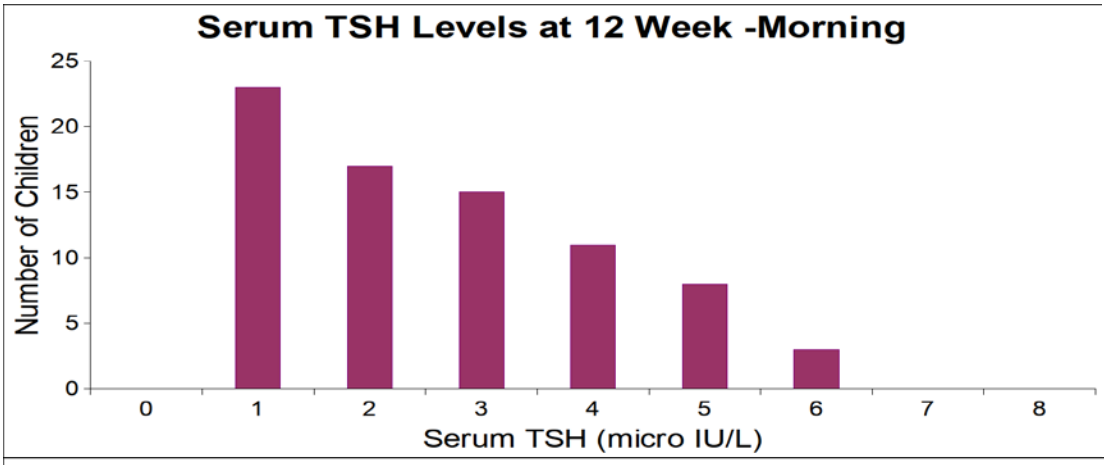
The sixth week mean systolic BP in Z score of bedtime group (0.14) is higher than morning group (-0.04). The difference in sixth week mean systolic BP in Z score of two group(-0.18) is statistically not significant (p=0.18).

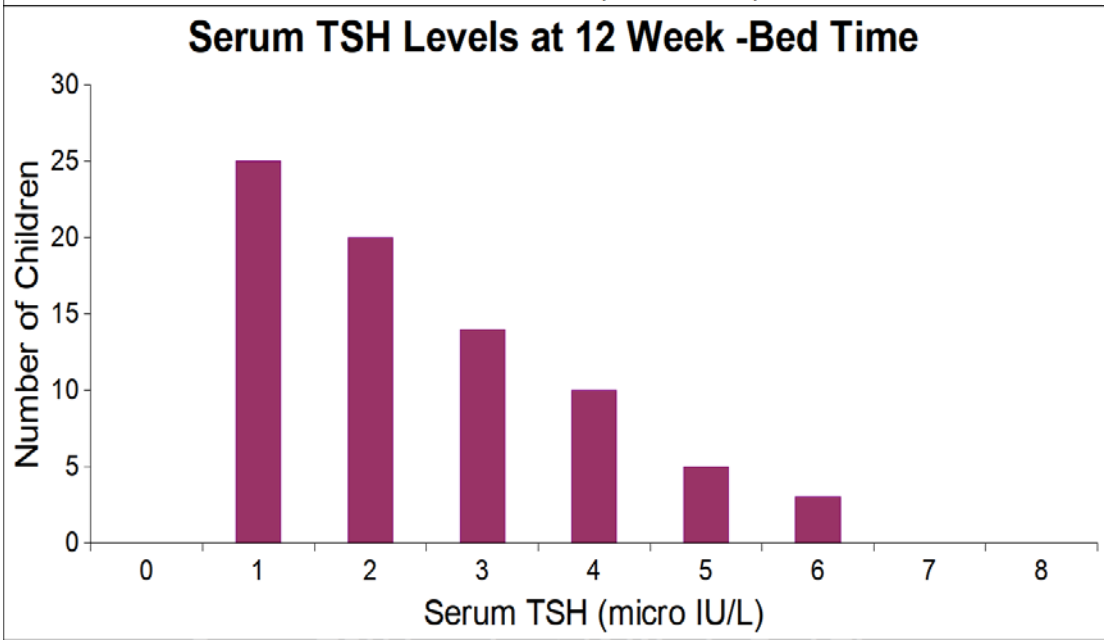




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.07±0.17	0.09	0.69	0.5
BED TIME	-0.02±0.20			

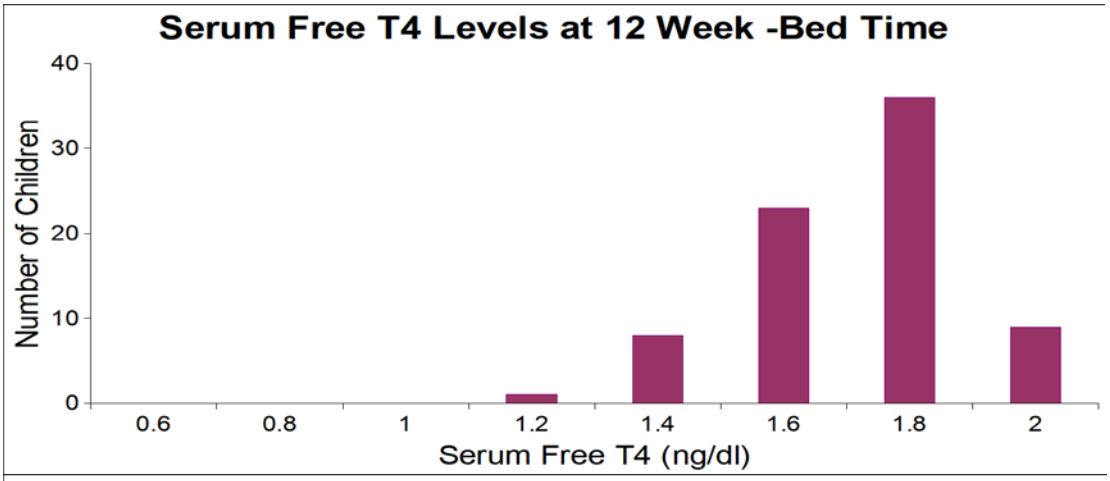
The sixth week mean diastolic BP in Z score of morning group (0.07) is higher than bedtime group (-0.02). The difference in sixth week mean diastolic BP in Z score of two group(0.09) is statistically not significant (p=0.5).

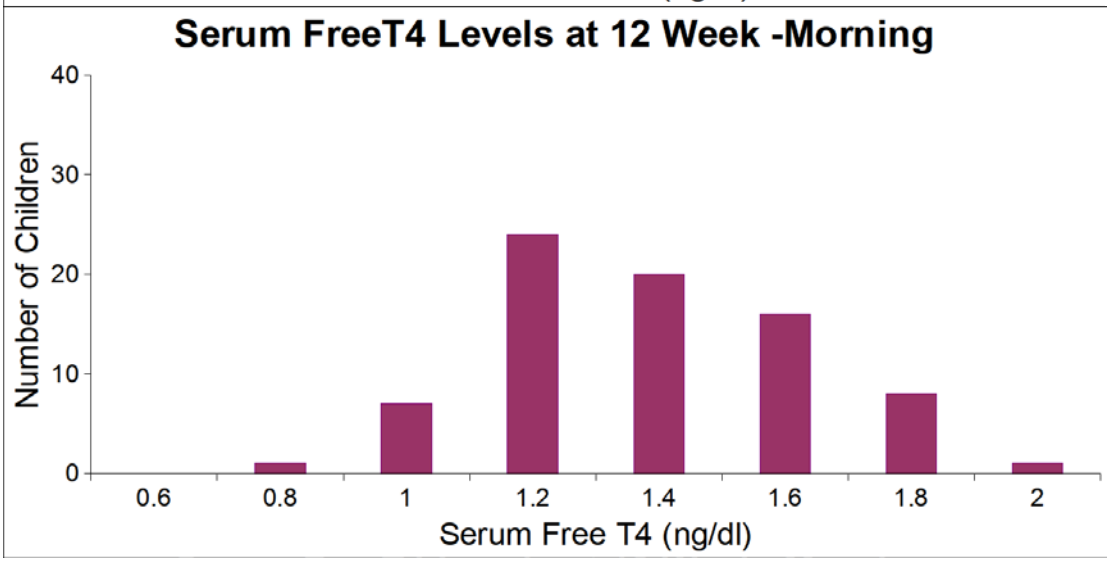




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	2.18±0.34	0.28	1.19	0.24
BED TIME	1.90 ± 0.33			

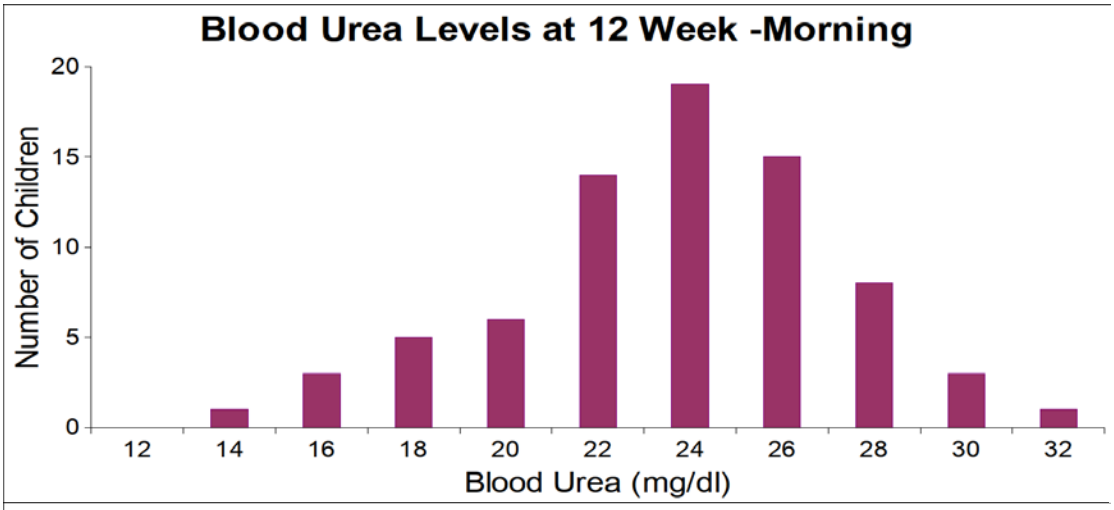
The twelfth week mean TSH level of morning group (2.18) is higher than bedtime group (1.90). The difference in twelfth week mean TSH level of two group(.028) is statistically not significant (p=0.24).

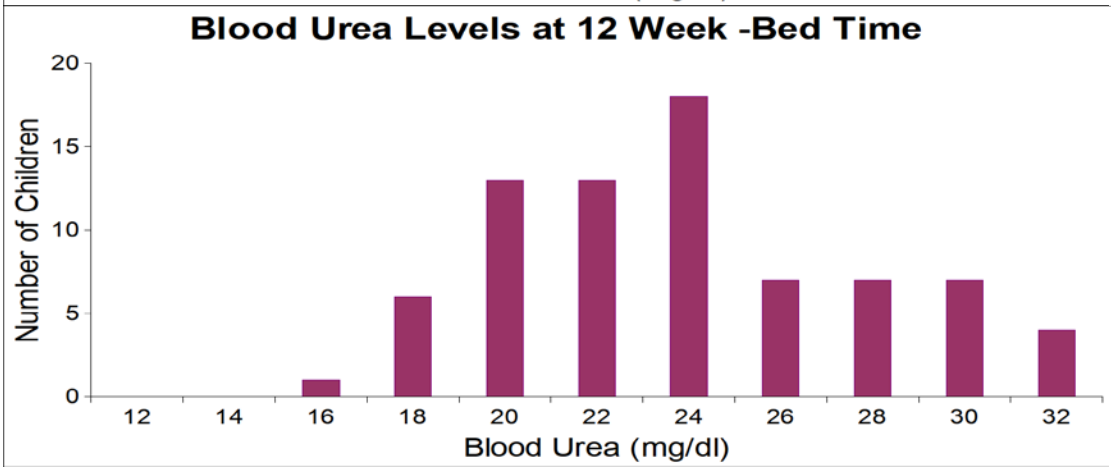




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	1.31 ± 0.06	-0.34	-9.33	<0.00001
BED TIME	1.65 ± 0.04			

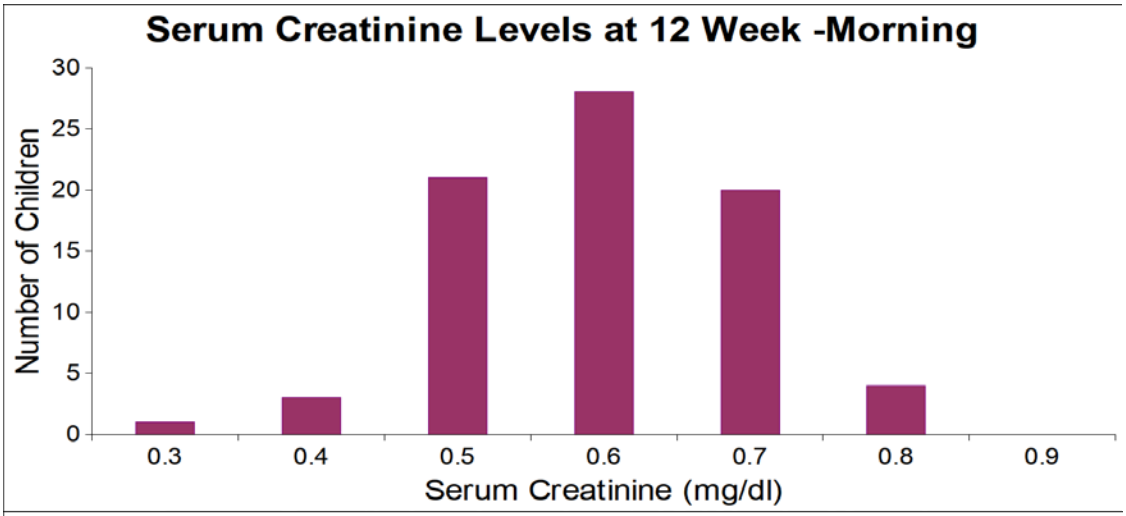
The twelfth week mean Free T4 level of bedtime group (1.65) is higher than morning group (1.31). The difference in twelfth week mean Free T4 level of two group(-0.34) is statistically significant ($p<0.00001$).

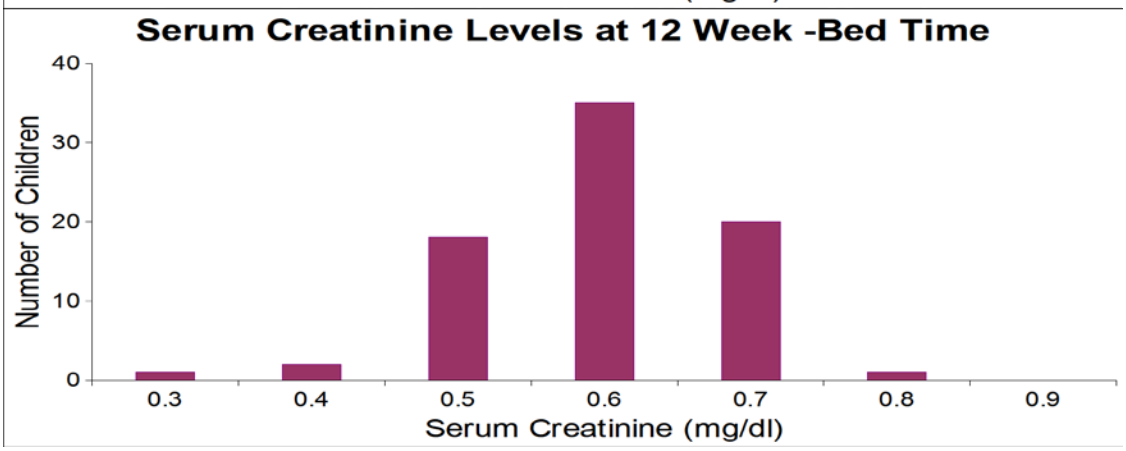




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	23.36 ± 0.88	-0.18	-0.28	0.78
BED TIME	23.54 ± 0.94			

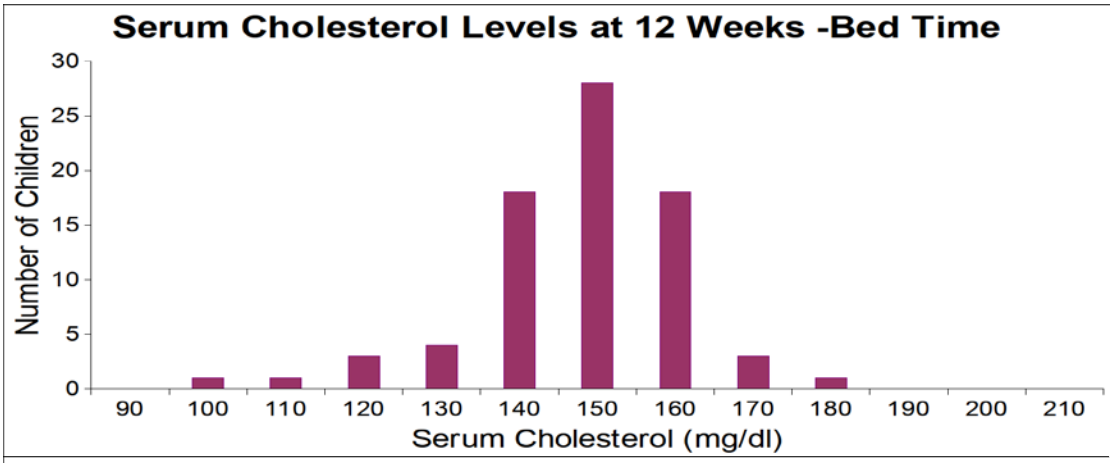
The tweflth week mean blood urea level of bedtime group (23.54) is higher than morning group (23.36). The difference in twelfth week mean blood urea level of two group(-0.18) is statistically not significant (p=0.78).

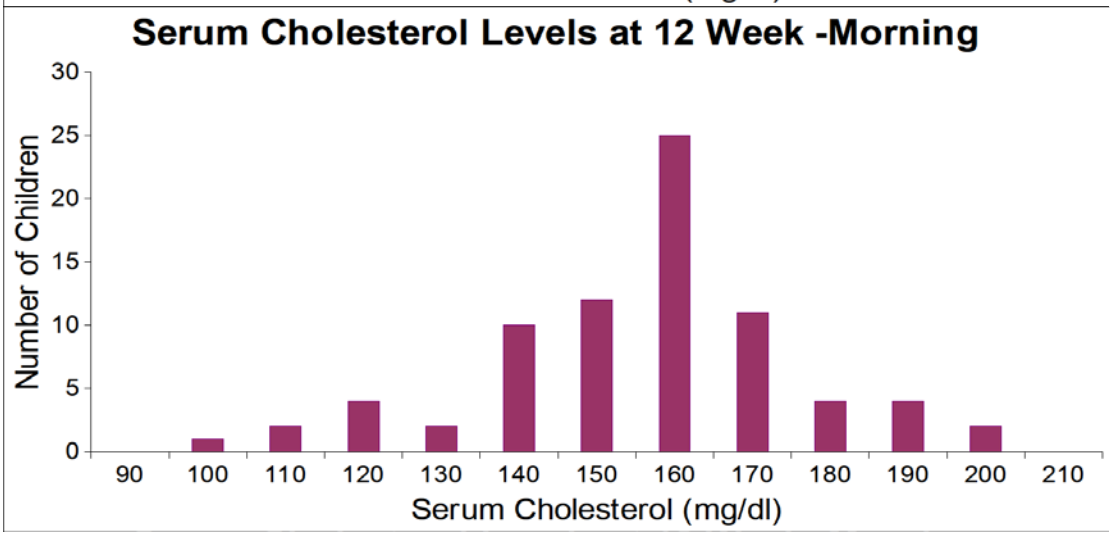




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.597 ± 0.02	0.001	0.08	0.93
BED TIME	**0.596 ± 0.02**			

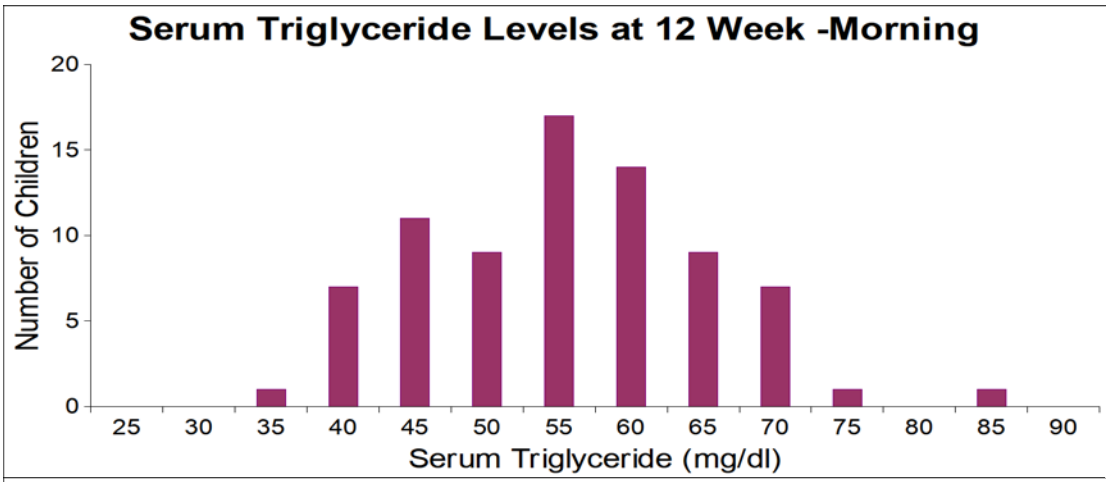
The twelfth week mean serum creatinine level of morning group (0.597) is higher than bedtime group (0.596). The difference in twelfth week mean serum creatinine level of two group(0.001) is statistically not significant (p=0.93).

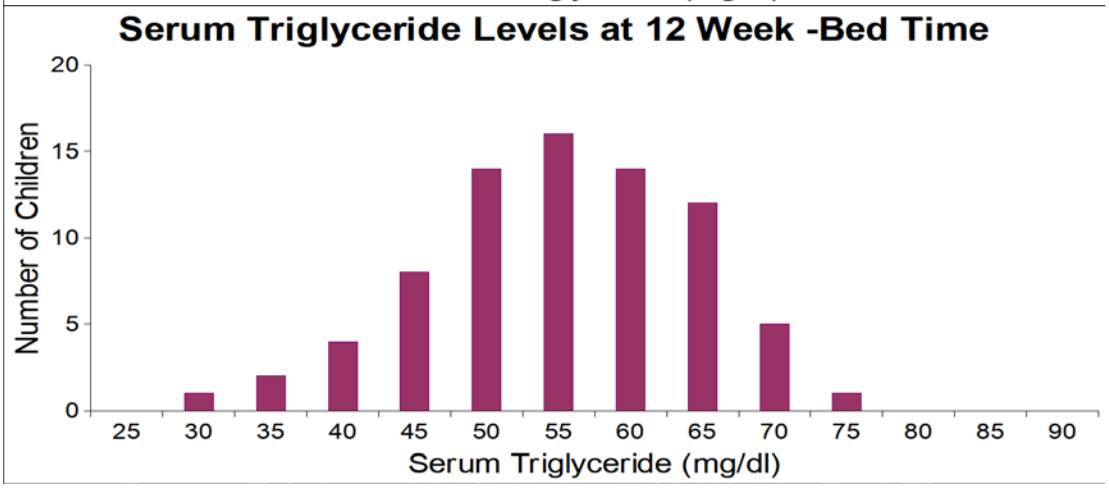




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	152.79 ± 4.59	9.21	3.34	0.001
BED TIME	143.58 ± 3.059			

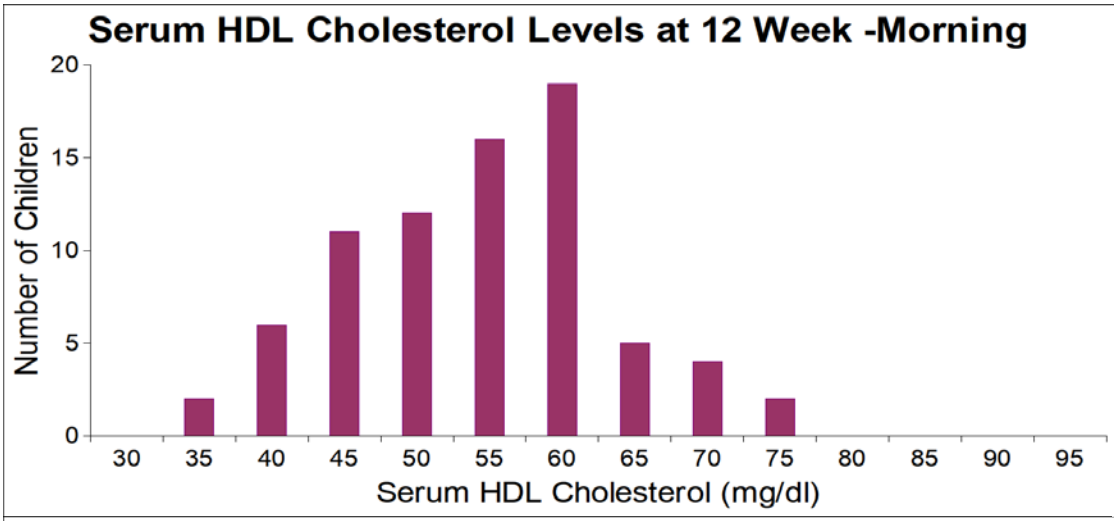
The twelfth week mean serum cholesterol level of morning group (152.79) is higher than bedtime group (143.58). The difference in twelfth week mean serum cholesterol level of two group(9.21) is statistically significant (p=0.001).

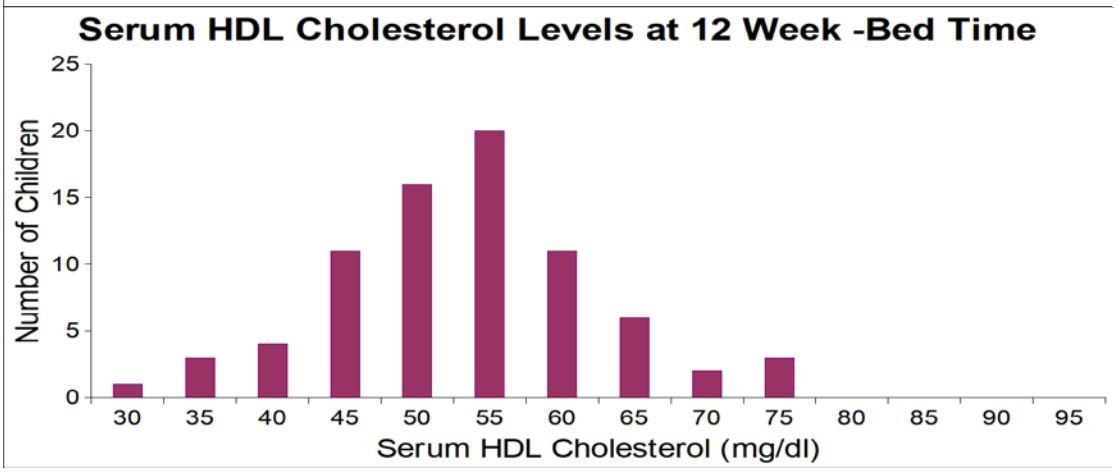




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	53.78 ± 2.21	0.61	0.40	0.69
BED TIME	53.17 ± 2.12			

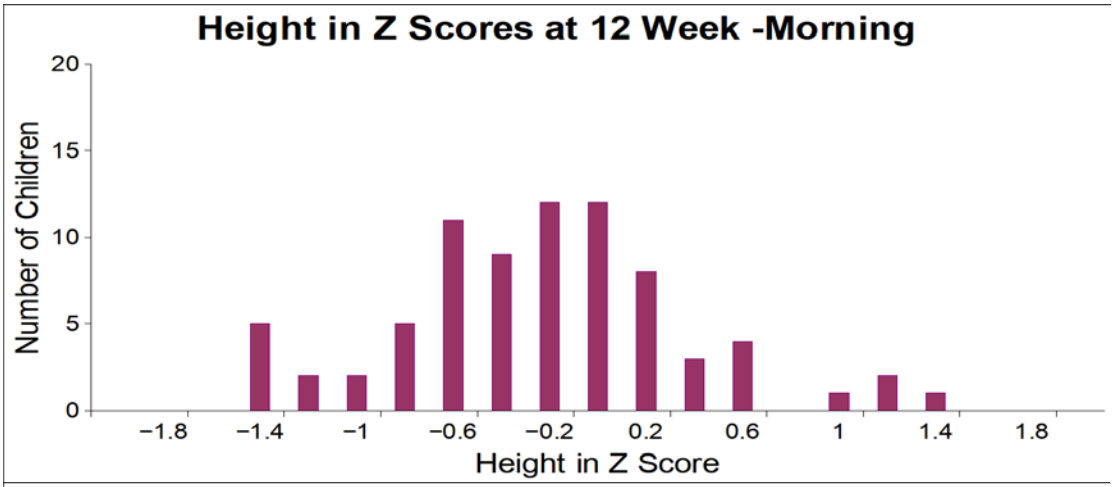
The twelfth week mean serum triglyceride level of morning group (53.78) is higher than bedtime group (53.17). The difference in twelfth week mean serum triglyceride level of two group(0.61) is statistically not significant (p=0.69).

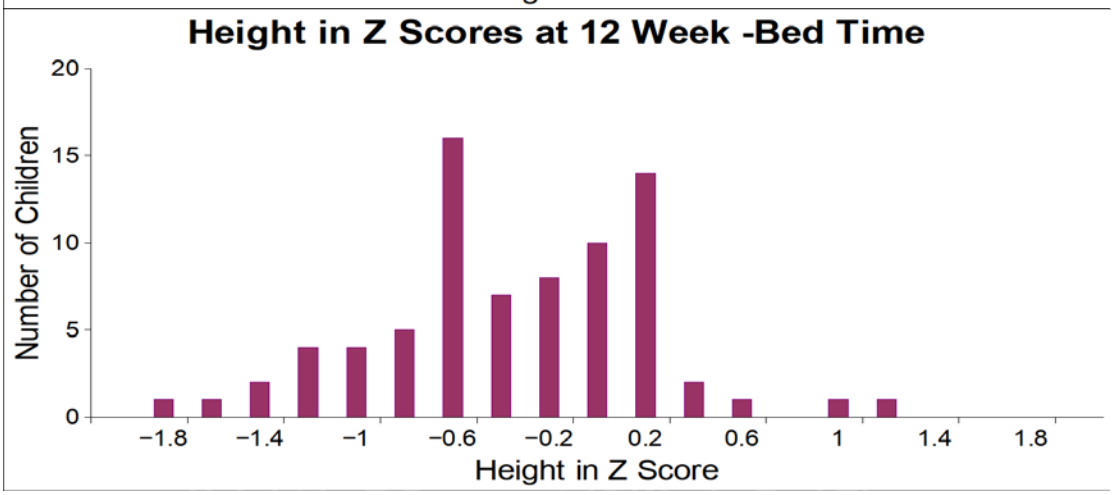




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	52.29 ± 2.04	0.82	0.55	0.58
BED TIME	51.47 ± 2.15			

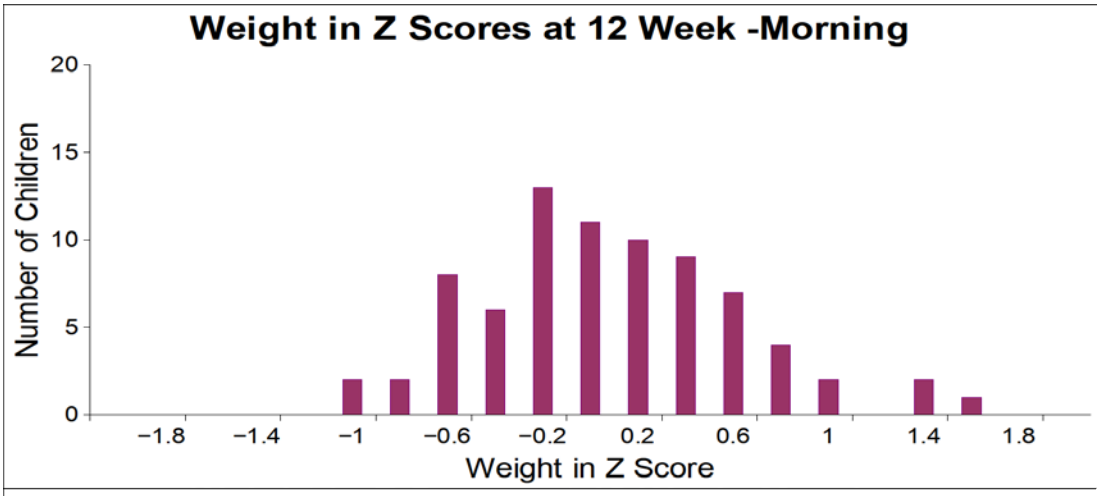
The twelfth week mean serum HDL cholesterol level of morning group (52.29) is higher than bedtime group (51.47). The difference in twelfth week mean serum HDL cholesterol level of two group (0.82) is statistically not significant (p=0.58).

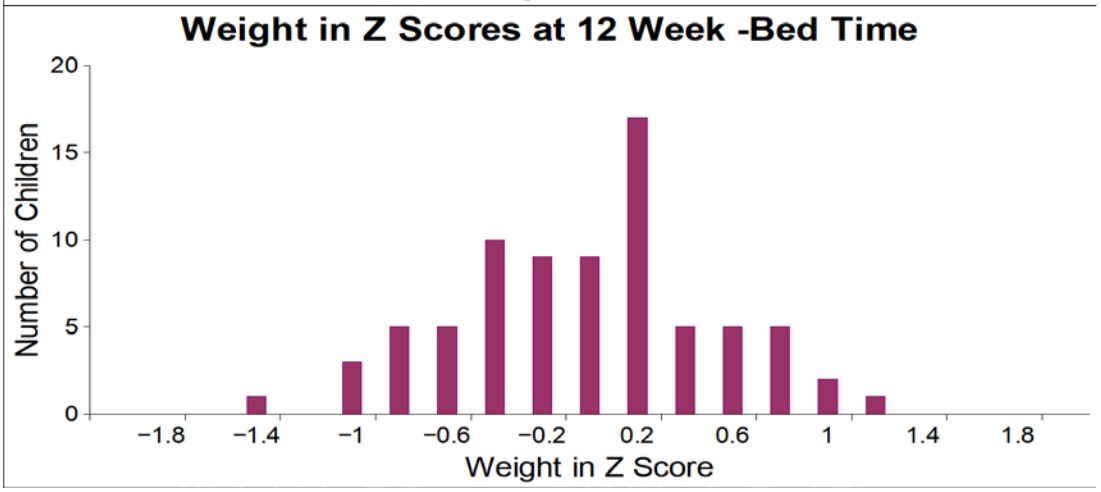




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.32 ± 0.13	0.11	1.14	0.25
BED TIME	-0.43 ± 0.13			

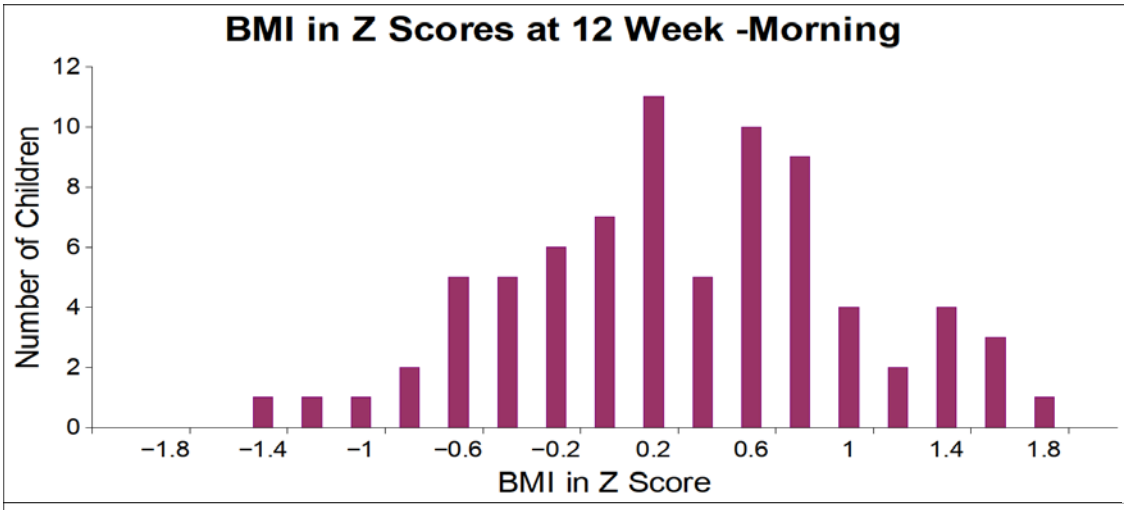
The twelfth week mean Height in Z score of morning group (-0.32) is higher than bedtime group (-0.43). The difference in twelfth week mean Height in Z score of two group(0.11) is statistically not significant (p=0.25).

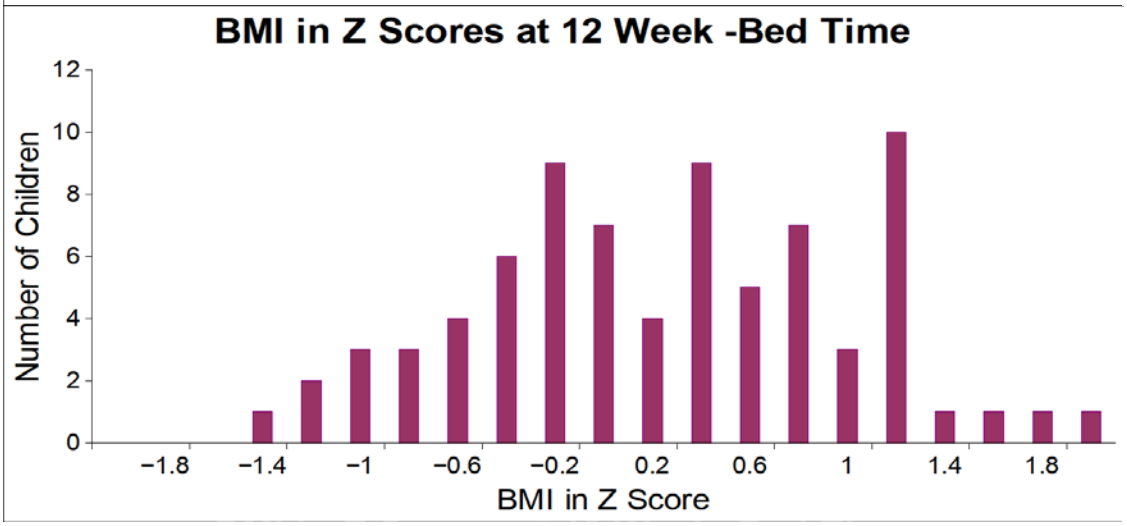




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.02 ± 0.12	0.01	1.17	0.25
BED TIME	-0.12 ± 0.12			

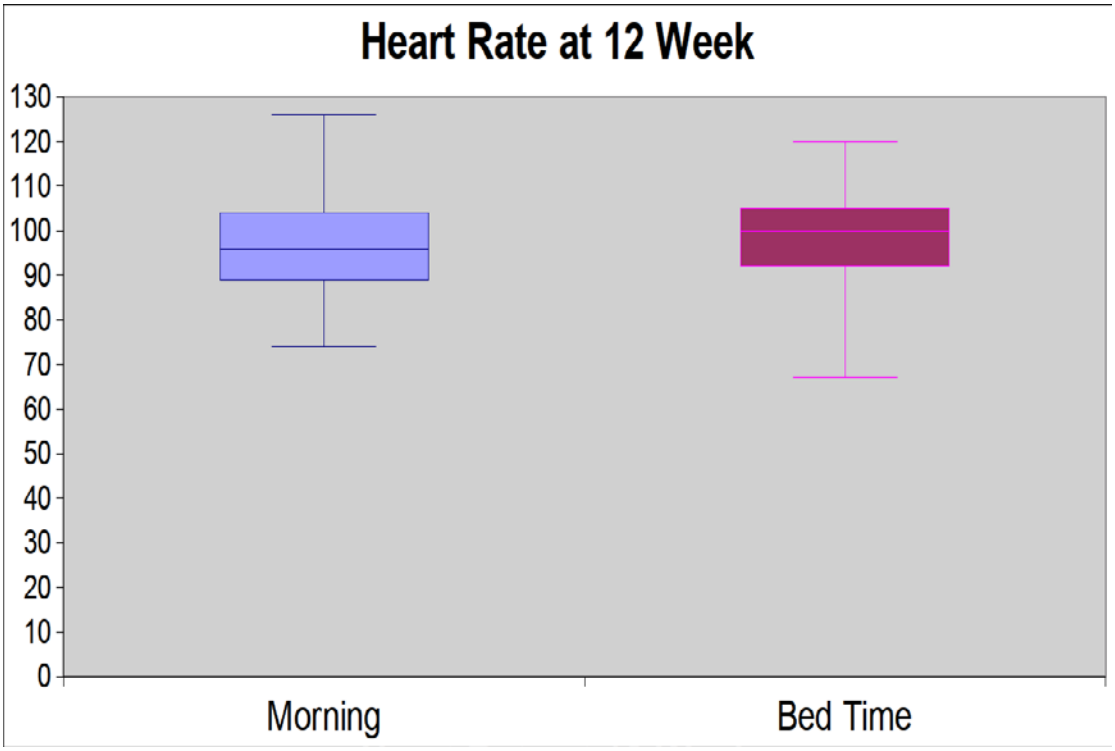
The twelfth week mean Weight in Z score of morning group (-0.02) is higher than bedtime group (-0.12). The difference in twelfth week mean Weight in Z score of two group(0.01) is statistically not significant (p=0.25).





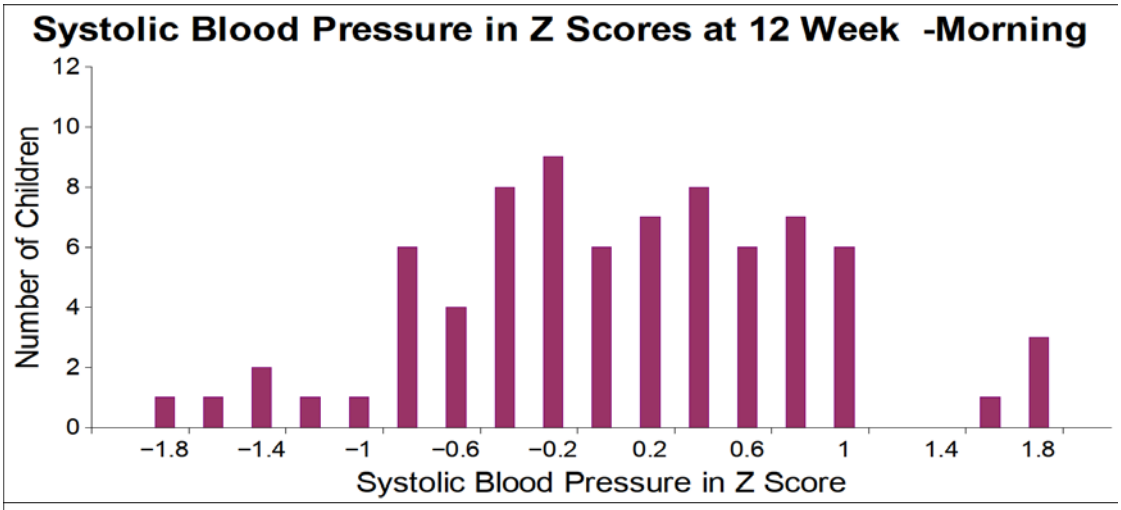
POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	0.22 ± 0.16	0.07	0.62	0.54
BED TIME	0.15 ± 0.18			

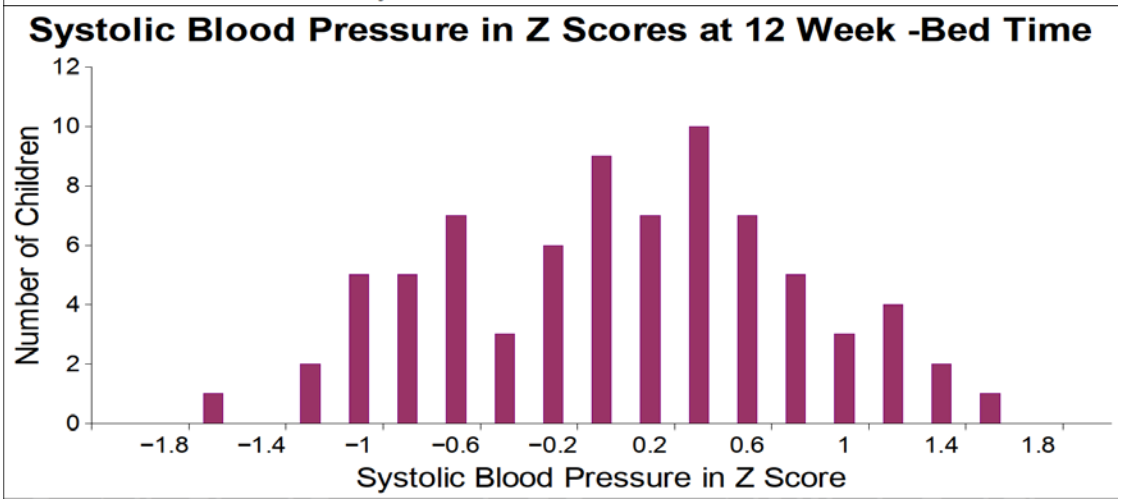
The twelfth week mean BMI in Z score of morning group (0.22) is higher than bedtime group (0.15). The difference in twelfth week mean BMI in Z score of two group(0.07) is statistically not significant (p=0.54).



POPULATION	MINIMUM	1ST QUARTILE	MEDIAN	MEAN	3RD QUARTILE	MAXIMUM
MORNING	74.00	89.00	96.00	96.87	104.00	126.00
BEDTIME	67.00	92.00	100.00	98.48	105.00	120.00

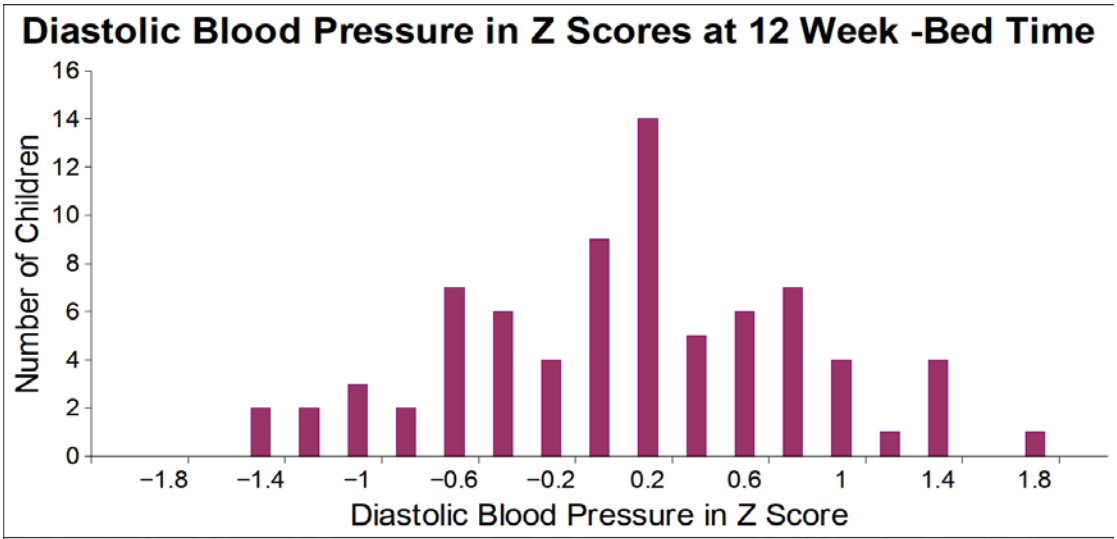
In morning group Heart rate ranged from 74 to 126. In bedtime group Heart rate ranged from 67 to 120. The difference in the mean Heart rate of these two groups is very minimal.

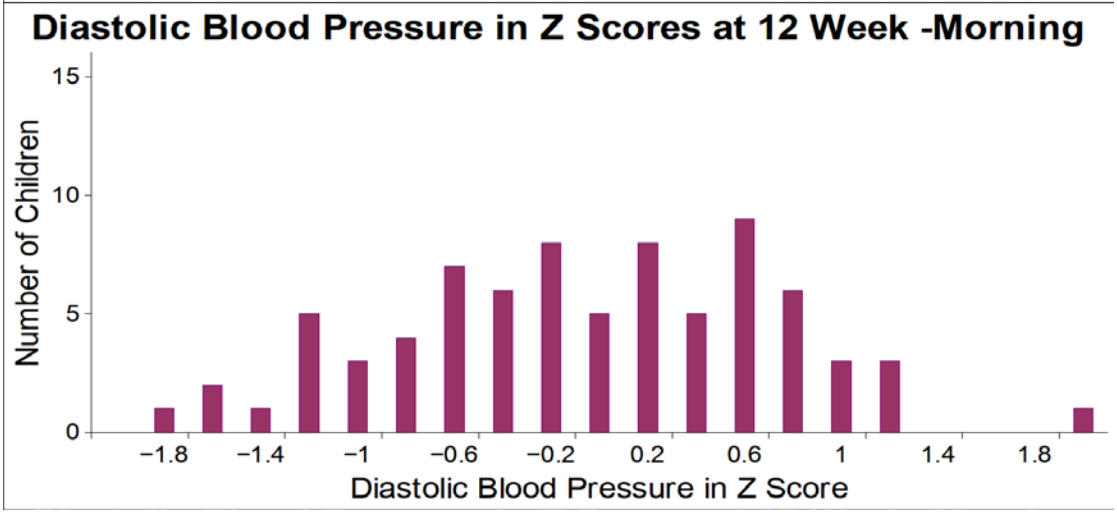




POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.024 ± 0.18	0.008	-0.07	0.94
BED TIME	-0.015 ± 0.16			

The twelfth week mean systolic BP in Z score of bedtime group (-0.015) is higher than morning group (-0.024). The difference in twelfth week mean systolic BP in Z score of two group(0.008) is statistically not significant (p=0.94).



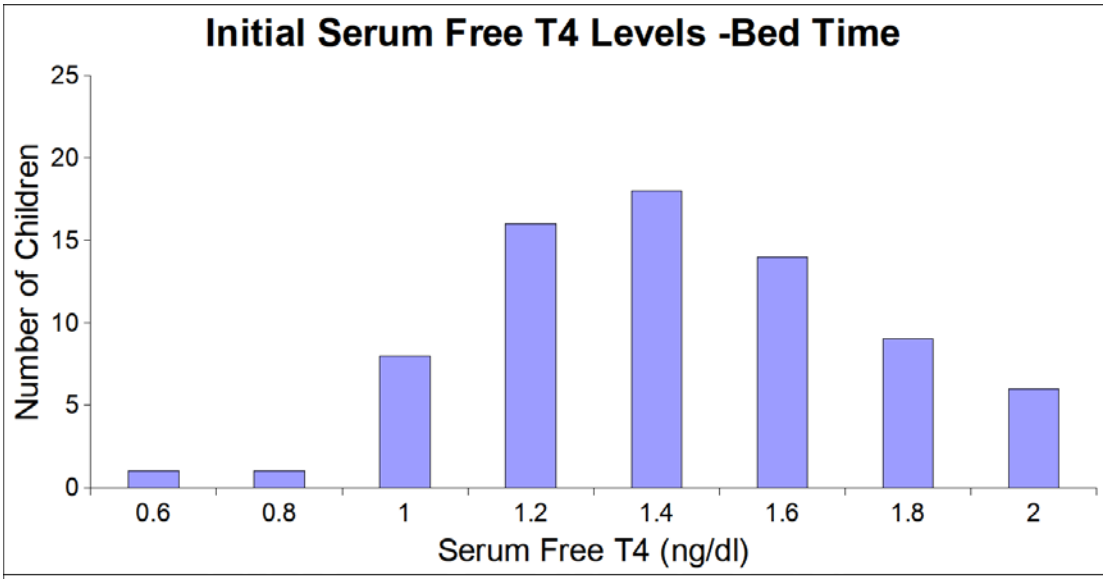


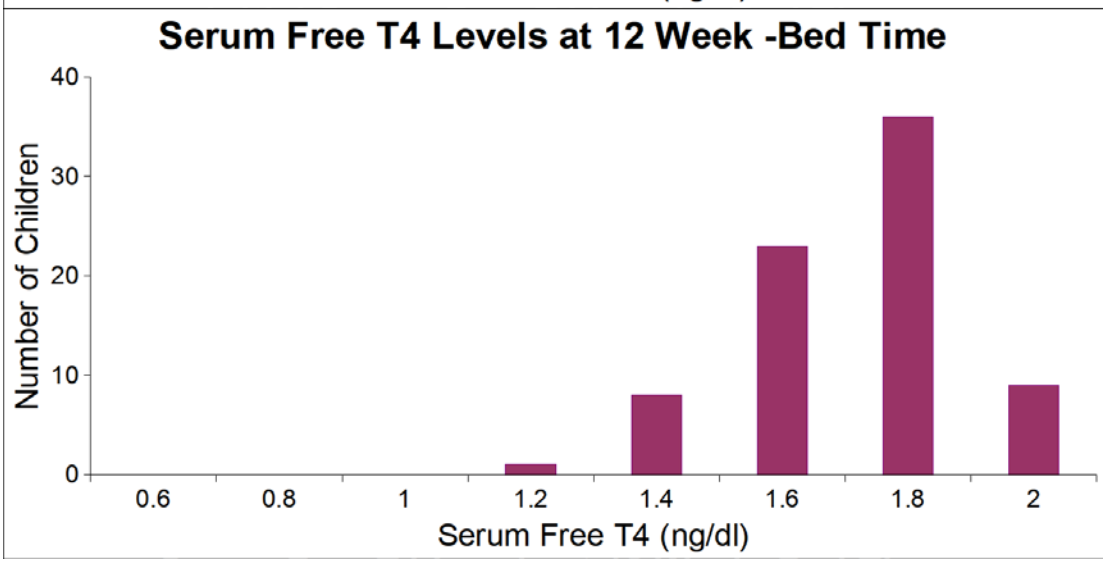
POPULATION	MEAN± 2 S.E	OBSERVED MEAN DIFFERENCE	T STAT	P VALUE
MORNING	-0.15 ± 0.18	-0.17	-1.4	0.16
BED TIME	0.02 ± 0.16			

The twelfth week mean diastolic BP in Z score of bedtime group (0.02) is higher than morning group (-0.15). The difference in twelfth week mean diastolic BP in Z scoe of two group(-0.17) is statistically not significant (p=0.16).

Intra group comparison of initial and twelfth week levels of various parameters of bedtime group

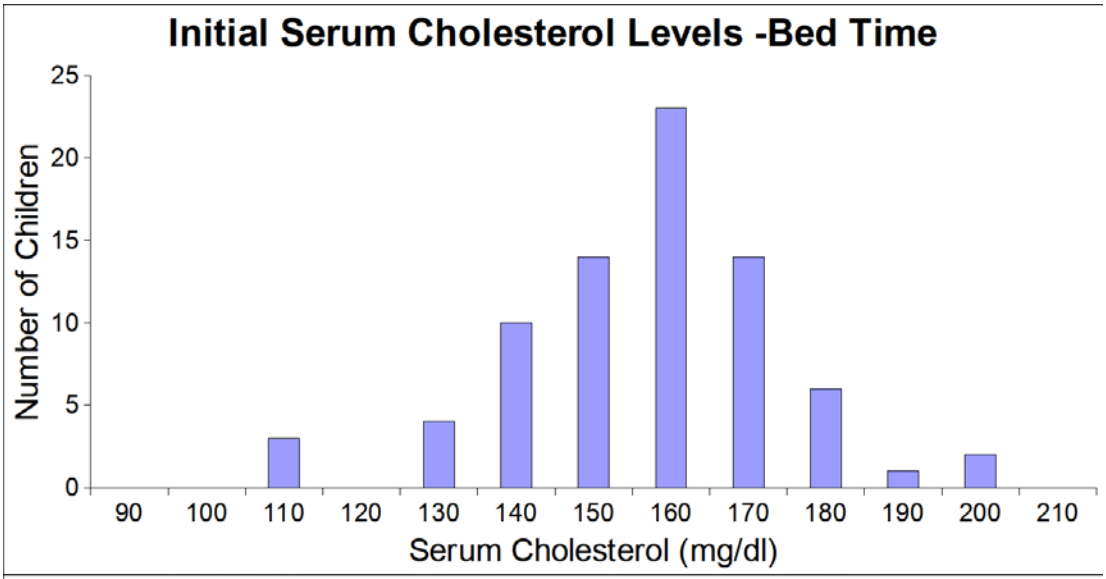
PARAMETER	0 Weeks	12 Weeks	P Value
TSH	1.93 ± 0.34	1.90 ± 0.33	0.91
FREE T4	1.40 ± 0.09	1.65 ± 0.04	<0.0001
UREA	23.70 ± 0.94	23.54 ± 0.94	0.80
CREATININE	0.59 ± 0.02	0.596 ± 0.02	0.80
CHOLESTROL	152.13 ± 4.14	143.58 ± 3.059	<0.0001
TRIGLYCERIDE	53.47 ± 2.16	53.17 ±2.12	0.84
HDL	51.79 ± 0.20	51.47 ± 2.15	0.83
HEIGHT	-0.40 ± 0.128	-0.437 ± 0.13	<0.0001
WEIGHT	-0.070 ± 0.12	-0.12 ± 0.12	<0.0001
BMI	0.19 ± 0.17	0.15 ± 0.18	<0.0001
SYSTOLIC BP	-0.03 ± 0.17	-0.015 ± 0.16	0.88
DIASTOLIC BP	-0.04 ± 0.18	0.02 ± 0.16	0.64

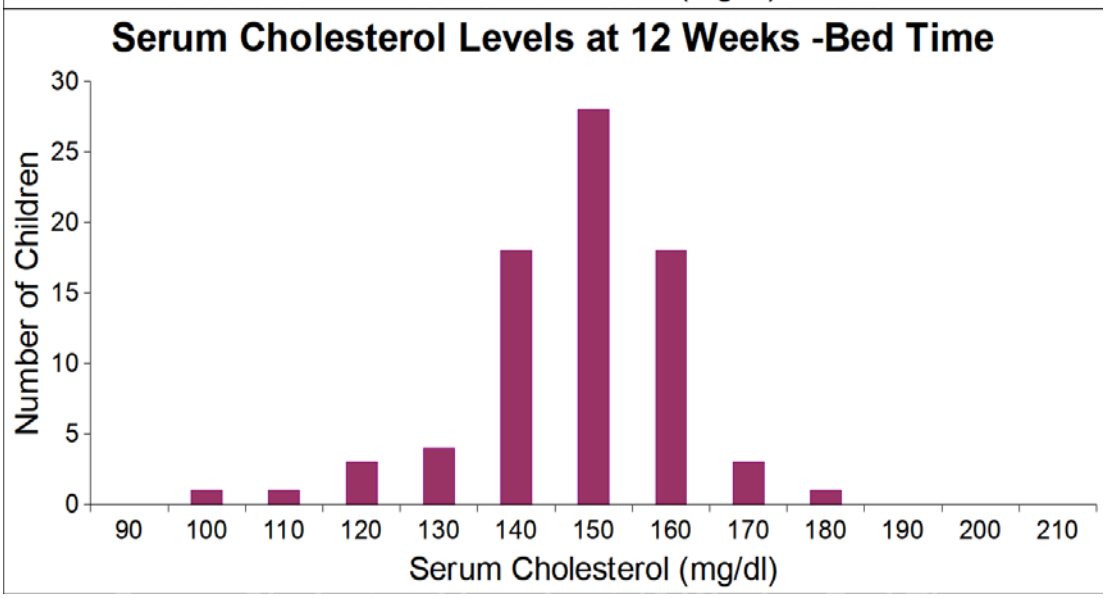




POPULATION	MEAN FREE T4 ± 2 SE	OBSERVED MEAN DIFFERENCE	P VALUE
INITIAL LEVEL	1.40 ± 0.09	0.25	<0.0001
TWELFTH WEEK LEVEL	1.65 ± 0.04		

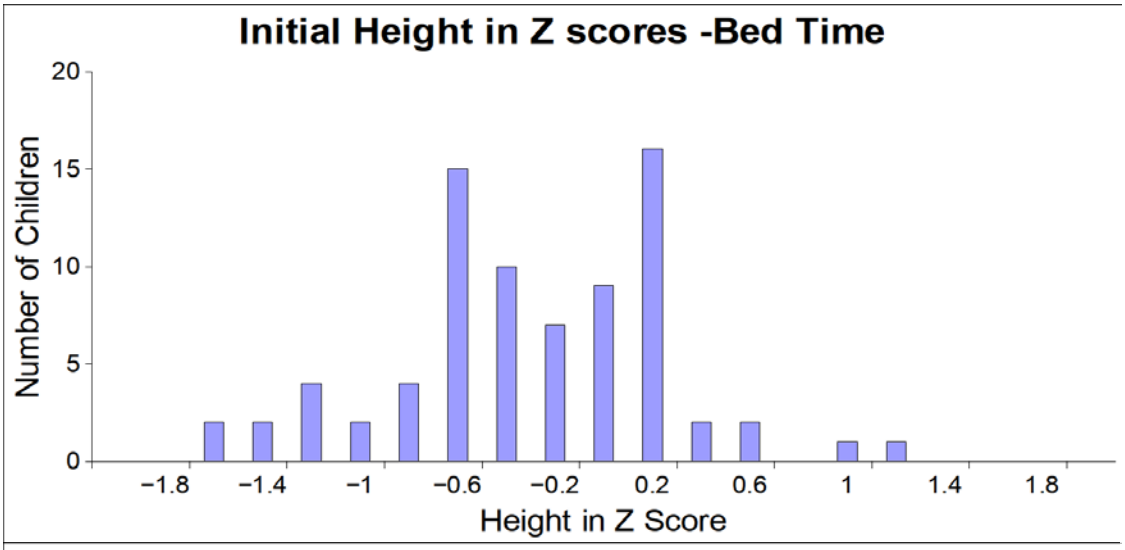
Difference in mean free T4 levels between these two group(0.25) is statistically significant($p<0.0001$)

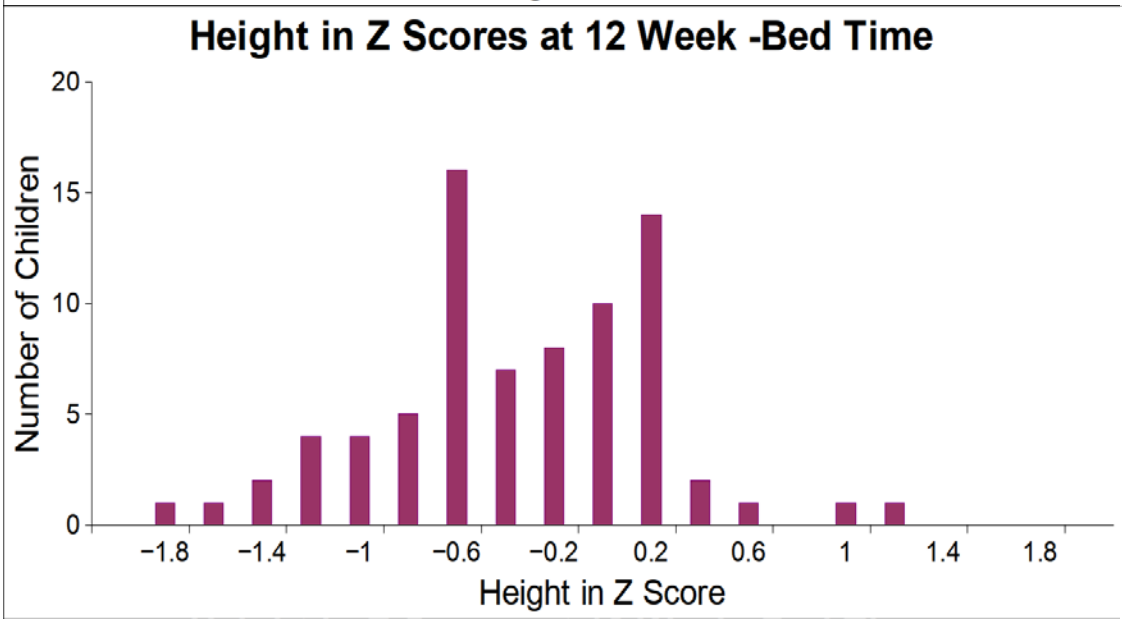




POPULATION	MEAN SERUM CHOLESTROL ± 2 SE	OBSERVED MEAN DIFFERENCE	P VALUE
INITIAL LEVEL	152.13 ± 4.14	8.55	<0.0001
TWELFTH WEEK LEVEL	143.58 ± 3.059		

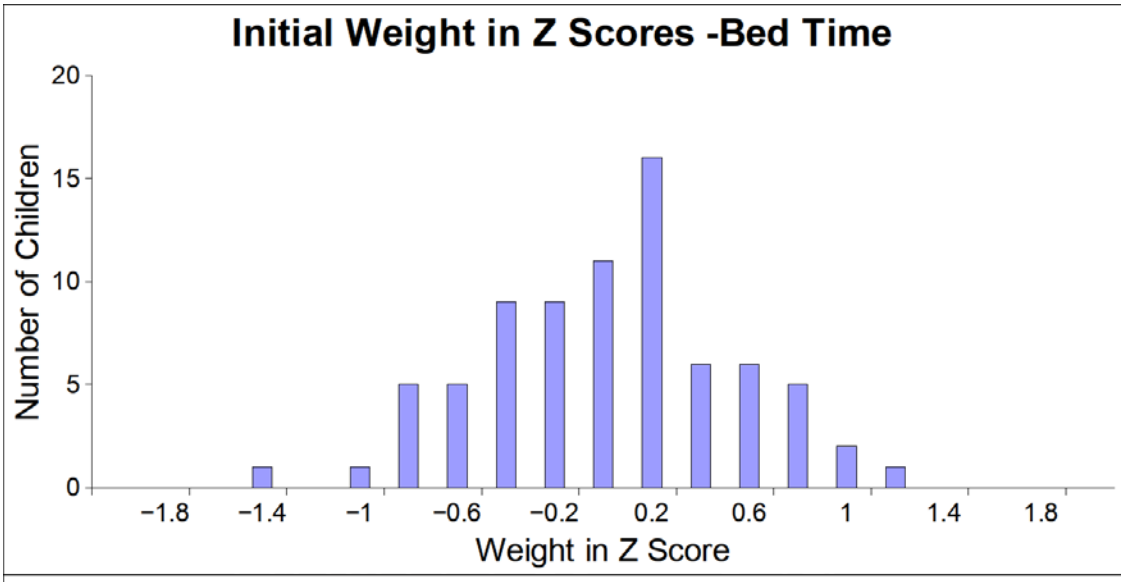
Difference in mean serum cholesterol levels between these two group(8.55) is statistically significant($p<0.0001$)

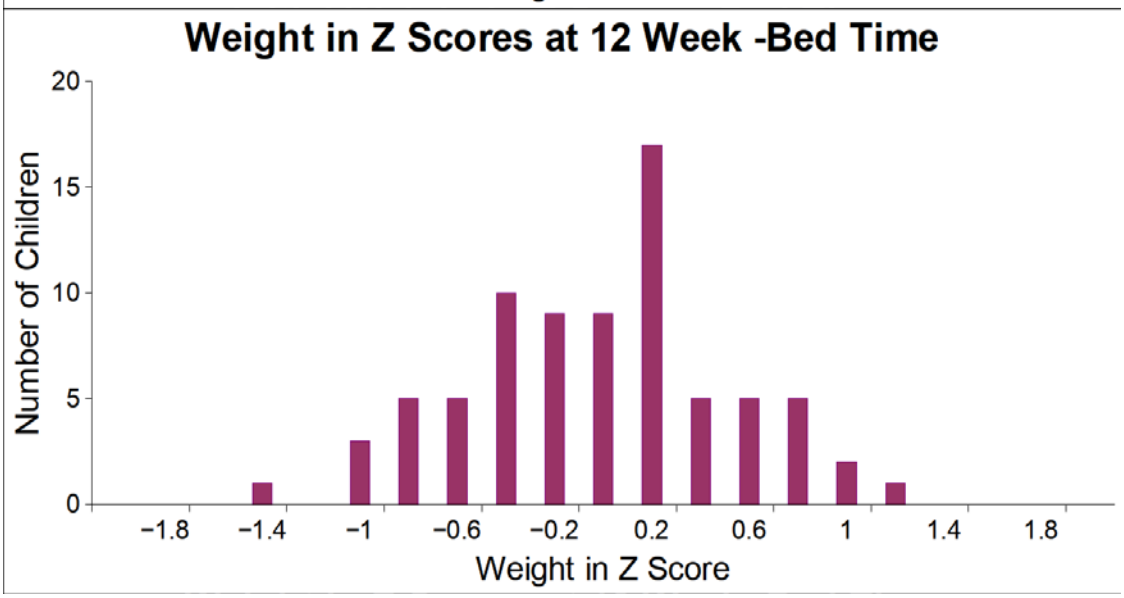




POPULATION	MEAN HEIGHT IN Z SCORE ± 2 SE	OBSERVED MEAN DIFFERENCE	P VALUE
INITIAL LEVEL	-0.40 ± 0.128	0.03	<0.0001
TWELFTH WEEK LEVEL	-0.43 ± 0.13		

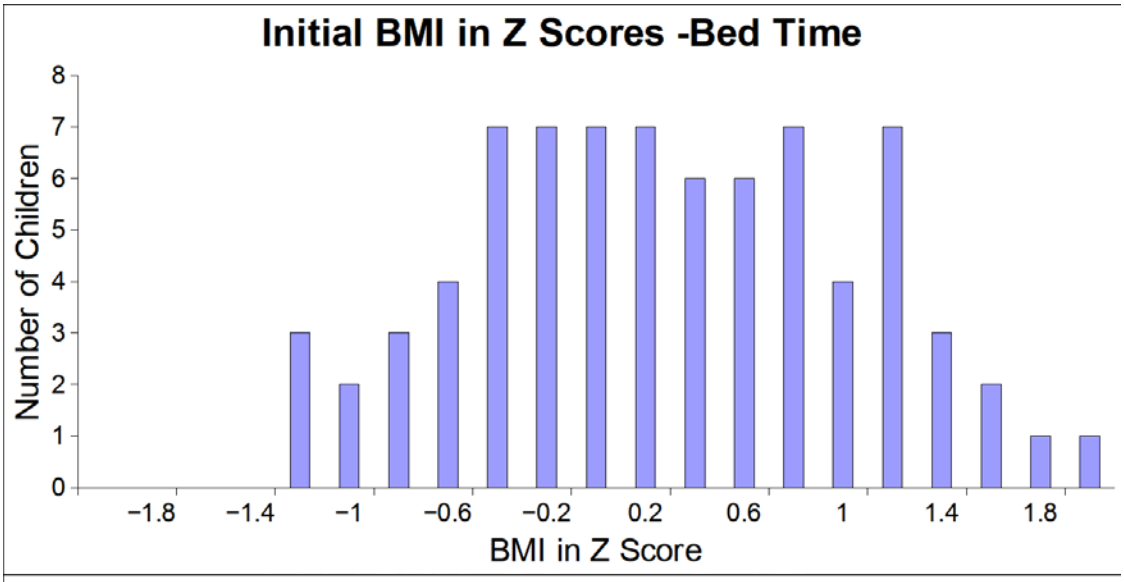
Difference in mean height in Z score levels between these two group(0.03) is statistically significant($p<0.0001$)

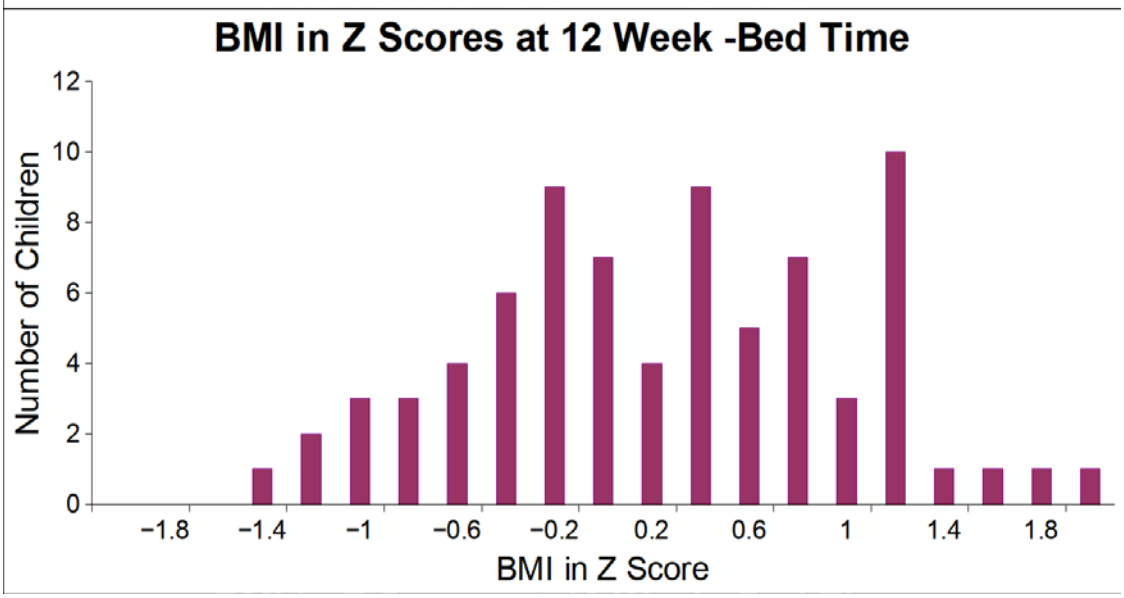




POPULATION	MEAN WEIGHT IN Z SCORE ± 2 SE	OBSERVED MEAN DIFFERENCE	P VALUE
INITIAL LEVEL	-0.07 ± 0.12	0.05	<0.0001
TWELFTH WEEK LEVEL	-0.12 ± 0.12		

Difference in mean weight in Z score levels between these two group(0.05) is statistically significant($p<0.0001$)





POPULATION	MEAN BMI IN Z SCORE ± 2 SE	OBSERVED MEAN DIFFERENCE	P VALUE
INITIAL LEVEL	0.19 ± 0.17	0.04	<0.0001
TWELFTH WEEK LEVEL	0.15 ± 0.18		

Difference in mean BMI in Z score levels between these two group (0.04) is statistically significant ($p<0.0001$)

DISCUSSION

For treatment of hypothyroidism, levothyroxine is supplemented in early morning in empty stomach because food intake interferes with levothyroxine absorption. Adherence to the timing of levothyroxine administration before breakfast is cumbersome in children, especially who are school going. The refusal of children and forgetfulness of parents are quite common, when parents are busy preparing the children for school. If proved evening dose of levothyroxine is equally efficacious as morning dose in children it will be useful for parents of hypothyroid children. Hence we performed this study to assess the effectiveness of bedtime levothyroxine administration as compared to morning levothyroxine administration. It is an open label randomized control study done in pediatric endocrinology department of ICH & HC, Chennai.

There are many studies done in adults to assess the effectiveness of morning levothyroxine administration versus bedtime levothyroxine administration with mixed results. To the best of our knowledge, this is the first pediatric study done till date to evaluate the effectiveness of bedtime levothyroxine as compared to morning levothyroxine administration.

At the start of study, all the demographic, clinical and biochemical parameters did not show any significant difference in both morning and bedtime group.

In our study mean age of children in morning group is 8.32 years and in bedtime group is 8.44 years. There is no statistically significant difference in mean age of two groups (p=0.8). Sex distribution ratio of male: female in

morning group is 0.51:1 and in bedtime group is 0.48:1. The difference in sex distribution among these two groups is not statistically significant (p=1).

Between the morning and bedtime group, the baseline level of TSH, free T4, blood urea, Serum creatinine, cholesterol, triglycerides, HDL cholesterol and Z scores of height, weight, BMI, systolic BP and diastolic BP do not show any statistical significant difference.

PARAMETERS	Morning (Mean±2SE)	Bed Time (Mean±2SE)	P VALUE
TSH	2.17±0.36	1.93±0.34	0.24
FREE T4	1.39±0.066	1.40±0.094	0.79
UREA	23.79±0.87	23.70±0.94	0.88
CREATININE	0.60±0.02	0.59±0.02	0.51
CHOLESTEROL	151.57±5.86	152.13±4.14	0.88
TGL	54.29±2.02	53.47±2.16	0.58
HDL	50.90±2.12	51.97±2.0	0.54
HEIGHT	-0.30±0.136	-0.40±0.128	0.28
WIGHT	0.03±0.12	-0.07±0.12	0.23
BMI	0.28±0.16	0.19±0.17	0.41
SYSTOLIC BP	-0.02±0.19	-0.03±0.17	0.91
DIASTOLIC BP	-0.05±0.18	-0.04±0.18	0.92

COMPARISON OF TSH LEVELS

In 6th week analysis, mean TSH level of morning group (2.35±0.38 mIU/L) and bedtime group (2.42±0.40 mIU/L) did not show any statistical difference (p=0.8). In 12th week analysis mean TSH level of morning group (2.18±0.34 mIU/L) and bedtime group (1.90±0.33 mIU/L) did not show any statistical difference (p=0.24). This finding is consistent with the study done by Nienke Bolk et al[1], Rajesh Rajput et al[4] and Elliot DP[8] but is in contrast to the study done by TG Bach-Huynh et al.

Nienke Bolk et al[1] conducted a randomised double blind cross over trial in 105 adult patients with primary hypothyroidism over a period of 6 months with switch over from morning to bedtime and viceversa at 3 months. The difference in TSH (at 12wks and 24wks) between morning (-0.92 mIU/L) and bedtime group (1.57 mIU/L) is statistically significant (p<0.001). Rajesh Rajput et al[4] conducted a clinical study in 2011. 152 newly diagnosed primary hypothyroid adults were chosen and divided into two groups (group 1 given levothyroxine in morning and group 2 at bedtime). Mean serum TSH levels between morning (5.13±9.36 mIU/L) and bedtime group (3.27±4.19 mIU/L) done at the end of 12wks did not show any statistical significant difference (p=0.31). Elliot DP[8] conducted a retrospective chart review in 2001. 15 elderly hypothyroid patients were chosen. The decrease in mean serum TSH level (0.286±1.722 mIU/L) when levothyroxine supplementation was changed from morning to midnight did not show any statistical significance (p=0.532). TG Bach-Huynh et al[3] conducted a randomised cross over study in 2009. 65 adult

study subjects were chosen and randomised into three 8wk regimens (fasting, bedtime, with breakfast) in a three period crossover design. Mean serum TSH levels was significantly high in bedtime group (2.19 mIU/L) when compared to before breakfast group (1.06 mIU/L) ($p<0.001$).

At 6 weeks, 2 children in morning group and 3 children in bed time group had marginal rise in their TSH levels. These values became normal at 12 weeks.

COMPARISON OF FREE T4

At 6^{th} week analysis, mean free T4 level of bedtime group (1.45 ± 0.08 ng/dl) is higher than morning group (1.33±0.2 ng/dl). This difference is statistically significant ($p= 0.03$). At 12^{th} week analysis, mean free T4 level of bedtime group (1.65±0.04 ng/dl) is higher than morning group (1.31±0.06 ng/dl). This difference is statistically significant ($p<0.00001$). These findings are consistent with the study done by Nienke Bolk et al[1], Rajesh Rajput et al[4] but contradictory to the study done by TG Bach-Huynh et al[3].

In Nienke Bolk et al[1] study, the difference in free T4 (at 12wks and 24wks) between morning (0.11 ng/dl) and bedtime group (-0.04 ng/dl) is statistically significant ($p=0.01$). In Rajesh Rajput et al[4] study, mean serum free T4 levels between morning (1.5±0.33 ng/dl) and bedtime group (1.48±0.31 ng/dl) done at the end of 12wks did not show any statistical significant difference ($p=0.31$). In T G Bach-Hyunh et al[3] study, free T4 value was less in bedtime group (1.34 ng/dl) when compared to morning group (1.35 ng/dl) but this difference is not statistically significant ($p=0.72$).

In our study the increase in mean free T4 value in bedtime group may be due to the better bioavailability of levothyroxine in bedtime (2 hours after dinner), decreased gastrointestinal movement during night time, more gastric acidity (circadian rhythm) in night and no food or drug intake after levothyroxine intake. In morning children usually wakeup very late and there is very less time gap between levothyroxine intake and breakfast. So there is less bioavailability of levothyroxine compared to bedtime group. Also snacks or other drug intake interferes with levothyroxine absorption. In hypothyroid children on levothyroxine, free T4 increases without any change of TSH.

COMPARISON OF RENAL PARAMETERS

At 6^{th} week, mean blood urea level of morning group (24.14±0.82 mg/dl) and bedtime group (23.79±0.86 mg/dl) did not show any statistical significant difference (p=0.56). At 12^{th} week, mean blood urea level of morning group (23.36±0.88 mg/dl) and bedtime group (23.54±0.94 mg/dl) did not show any statistical significant difference (p=0.78).

At 6^{th} week, mean serum creatinine level of morning group (0.6±0.02 mg/dl) and bedtime group (0.59±0.02 mg/dl) did not show any statistical significant difference (p=0.57). At 12^{th} week, mean serum creatinine level of morning group (0.597±0.02 mg/dl) and bedtime group (0.596±0.02 mg/dl) did not show any statistical significant difference (p=0.93). This finding is consistent with the study done by Nienke Bolk et al[1] in which the difference in serum creatinine level (at 12wks and 24wks) between morning (-0.03 mg/dl) and bedtime group (0.00 mg/dl) did not show any statistically significant

difference (p=0.13). The possible explanation may be that, alteration in renal function occurs only in chronic uncontrolled hypothyroid subjects but in our study all children were in euthyroid state at the start of study and throughout the study.

COMPARISON OF LIPID PROFILE

At 6 weeks, mean serum cholesterol, triglycerides, HDL cholesterol of morning group (151.17±5.6mg/dl, 53.88±1.92mg/dl, 53.95±1.98mg/dl) and bedtime group (147.71±5.82mg/dl, 54±2.56mg/dl, 53.57±1.8mg/dl) did not show any statistical significant difference.

A 12 weeks, the difference in mean serum cholesterol of morning group (152.79±4.59 mg/dl) and bedtime group (143.58±3.059 mg/dl) is statistically significant (p=0.001). This may due to the better bioavailability of levothyroxine at bedtime that stimulates the expression of hepatic LDL receptor and metabolism of cholesterol to bile acids that lead to decrease in mean cholesterol level in bedtime. This finding is contradictory to the study done by Rajesh Rajput et al[4] in which there was no significant difference in serum cholesterol levels between morning and bedtime group. Also in the study done by Nienke Bolk et al[1], there was no significant difference in serum cholesterol levels between morning and bedtime group (p=0.22).

At 12 weeks, mean serum triglycerides and HDL cholesterol of morning group (53.78±2.21 mg/dl, 52.29±2.04 mg/dl) and bedtime group (53.17±2.12 mg/dl, 51.47±2.15 mg/dl) did not show any statistical significant difference (p=0.69,p=0.58). This is similar to the study done by Rajesh Rajput et al[4] in

which there was no significant difference in serum triglyceride and HDL levels between morning and bedtime group.

COMPARISON OF ANTHROPOMETRIC PARAMETES

At 12 weeks, anthropometric indices like height, weight and BMI in Z score of morning group (-0.32±0.13, -0.02±0.12, 0.22±0.16 respectively) and bedtime group (-0.43±0.13, -0.12±0.12, 0.15±0.18 respectively) did not show any statistical significant difference (p=0.25, p=0.25, p=0.54 respectively). This finding is similar to the study done by Nienke Bolk et al[1], in which there was no significant difference in BMI between morning and bedtime group (p=0.09).

COMPARISON OF VITAL PARAMETERS

At 6 weeks, the mean heart rate in morning group was 99.04 beats/min and in bedtime group was 98.43 beats/min. The mean Z score of Systolic BP and Diastolic BP of morning group (-0.04±.18, 0.07±0.17) and bedtime group (0.14±0.18, -0.02±0.20) did not show any statistical significant difference (p=0.18 and 0.5 respectively).

At 12 weeks, the mean heart rate in morning group was 96.84 beats/min and in bedtime group was 98.48 beats/min. In Nienke Bolk et al[1] study, there was no significant difference in heart rate between morning and bedtime group (p=0.40). The mean Z score of Systolic BP, Diastolic BP of morning group (-0.024±0.18, -0.15±0.18) and bedtime group (-0.015±0.16, 0.02±0.16) did not show any statistical significant difference (p=0.94 and 0.16 respectively).

INTRAGROUP COMPARISON

In intragroup comparison of bedtime group at initial and 12th week levels show following significance. In bedtime group, the difference in mean free T4 level at 0 weeks (1.40±0.09ng/dl) and 12 weeks (1.65±0.04ng/dl) is statistically significant ($p<0.0001$). This is similar to the study done by Rajesh Rajput et al[4] in which intragroup comparison of free T4 levels at 0weeks (0.74±0.5 ng/dl) and 12weeks (1.48±0.31 ng/dl) in bedtime group showed statistical significant difference ($p<0.0001$).

In bedtime group, the difference in mean cholesterol level at 0 weeks (152.13±4.14) and 12th week (143.52±3.059) is statistically significant ($p<0.0001$). This is similar to the study done by Rajesh Rajput et al[4] in which intragroup comparison of mean cholesterol levels at 0weeks (196.88±75.69 mg/dl) and 12weeks (173.85±38.25 mg/dl) in bedtime group showed statistical significant difference ($p=0.015$).

Anthropometry indices like height, weight and BMI in Z score of bedtime group measured at 0 week (-0.40±0.128,-0.070±0.12, 0.19±0.17) in comparison to 12th week (-0.43±0.13, -0.12±0.12, 0.15±0.18) showed statistical significant difference ($p<0.0001$, $p<0.0001$, $p<0.0001$).

The mean Z score in weight and BMI have reduced at 12th week when compared to 0 weeks in bedtime group. The decrease in their mean is statistically significant but mean Z score for height has also reduced at 12 weeks when compared to 0 week. As BMI has not increased, the clinical

significance of reduction in Z score of height is not discernible. The reduction in Z score of height may be due to short time follow up and observer error.

T½ of levothyroxine is seven days, so follow up assessment of thyroid hormone profile and other secondary outcomes were measured at six weeks and to overcome the “carry over effect”, assessment of thyroid hormone profile was extended to 12th week. In Nienke Bolk et al[1] study, assessment of primary and second outcome was measured at twelfth and twenty fourth weeks. In T G Bach-Huynh et al[3] study, assessment of primary and secondary outcome was done at eighth, sixteenth and twenty fourth week. In Rajesh rajput et al[4] study, assessment of primary and secondary outcome was done in sixth and twelfth week and mainly intra group comparison was done.

In our study, same dosage of levothyroxine was maintained in all children throughout the study. However the cause of hypothyroidism was not taken into account since irrespective of the cause being congenital or acquired, dosage of levothyroxine supplementation was calculated only based on the age and weight of the child and does not differ depending on the cause.

CONCLUSION

The dosage of levothyroxine which maintained euthyroid status (as reflected by TSH and fT4 level) when taken in early morning empty stomach is also likely to maintain euthyroid status when it is administered at bedtime. There is a significant improvement in free T4 level when levothyroxine was taken at bedtime. There is considerable decrease in serum cholesterol level when levothyroxine was taken at bedtime.

Effects of bedtime levothyroxine administration on anthropometry, vital parameters and other parameters in lipid profile are comparable to those observed in children taking morning levothyroxine.

LIMITATIONS

The ideal design would have been cross over design providing adequate time to nullify the carry over effect.

To assess the real impact of bedtime levothyroxine on anthropometric parameters, a longer prospective follow up may be needed.

We failed to employ any scale to assess the quality of life and symptom alleviation.

RECOMMENDATIONS

The efficacy of bedtime regimen of levothyroxine is quite comparable to the efficacy of morning regimen. Bedtime regimen may result in good compliance in school going children. Parents should be allowed to choose either morning or bedtime regimen depending on their convenience.

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PROFORMA

l. Study Id:

2. Name:

3.OP Number:

4.Age: DOB-

Actual age- _____ years_____months

5.Sex: A)Male B)Female

EXAMINATION

1.Height

2.Weight

3.Body mass index

4.Heart rate

5.BP

INVESTIGATIONS

1.TSH

2.Free T4:

3.Lipid profile

4.Creatinine level

PATIENT INFORMATION SHEET

Place of study: Institute Of Child Health And Hospital for Children, Egmore, Chennai-8.

Name of Investigator: Dr.RADHAKRISHNAN.R

Name of Participant: A**ge**: S**ex**:

Hospital No:

Study title: EFFECTIVENESS OF BEDTIME LEVOTHYROXINE INTAKE AS COMPARED TO STANDARD REGIMEN IN CHILDREN"

We request y our child to participate in the study.

Aim of the study-

To assess effectiveness of morning Levothyroxine administration as compared to bedtime Levothyroxine administration to bring down thyrotropin level in hypothyroid children

Methods-

In order to find out effect of bedtime levothyroxine intake , we will be examining your child, measure his height, weight,HR,BP and BMI and we will be drawing 5ml blood to look for TSH,free T4,lipid level and creatinine.

Can I refuse to participate in the study?

Participation in the study is purely voluntary. You may refuse to participate or withdraw from the study at any time. In both cases the treatment and care your child receives from this hospital will not be affected in any manner.

Benefits and harms of participating in the study-

Your child will not benefit directly by participating in this study. But by way of participating in this study, your child is contributing to

updation of science which may benefit her/him and all other patients with this disease in future.

Confidentiality-

The data collected from the study will be used for the purpose of study only. The results of the study will be published. Personal information of the children participating in the study will be kept confidential. There will not be any disclosure about your child's information without your permission.

Subject rights-

If you wish further information regarding your child's rights as a research participant, you may contact the principal investigator in the mobile number or address mentioned below.

Principal Investigator – Dr Radhakrishnan.R

Mobile number - 9629596767

Contact Address - MD 2nd yr Post Graduate, Institute of Child Health and Hospital for Children, Halls Road, Egmore, Chennai.

Place:

Date: Signature of Parent

INFORMED CONSENT FORM

Study place: Institute Of Child Health And Hospital For Children,
Egmore, Chennai-8.

Title of the study : "EFFECTIVENESS OF BEDTIME LEVOTHYROXINE INTAKE AS COMPARED TO STANDARD REGIMEN IN CHILDREN".

Name of the investigator: Dr. RADHAKRISHNAN.R

Name of the Participant: **Age**: **Sex**:
Hospital number:

1. I have read and understood the patient information sheet provided to me regarding the participation of my child in the study.
2. I have been explained about the nature of the study and had my questions answered to my satisfaction.
3. I have been explained about my rights and responsibilities by the investigator.
4. I will allow my child to cooperate with the investigator and undergo clinical tests subjected during the study whole heartedly.
5. I have been advised about the risks associated with my child's participation in this study.
6. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my child's future treatment in this hospital.
7. I hereby give permission to the investigators to release the information obtained from my child as result of participation in this study to medical journals/conference proceedings.
8. I understand that my child's identity will be kept confidential if my child's data are publicly presented/published.
9. I have decided my child can participate in the research study. I am aware that if I have any question during this study, I should contact the investigator.
10. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the parent/guardian
Name _____ Signature_____

Date_____

Name and Signature of the investigator
Name _____ Signature_____

Date_____

Name and Signature of impartial witness 1:
Name _____ Signature_____

Date_____

Name and Signature of impartial witness 2:
Name _____ Signature_____

Date_____

ஆராய்ச்சியில் பங்கு பெறுவோர்கான தகவல் படிவம்

ஆராய்ச்சி நடத்தப்படும் இடம்	:	அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8
முதன்மை ஆராய்ச்சியாளர்	:	மரு. ஆர்.ராதாகிருஷ்ணன்
பங்கேற்பவர் பெயர்	:	வயது பாலினம்

மருத்துவமனை எண்:

ஆய்வின் தலைப்பு	:	குழந்தைகளுக்கு தைராக்ஸின் மாத்திரையை வழக்கமாக காலையில் கொடுப்பதற்கு பதில் இரவில் கொடுப்பதால் ஏற்படும் மாற்றங்கள் பற்றிய ஆய்வு

நாங்கள் உங்கள் குழந்தையை இந்த ஆய்வில் பங்கெடுக்குமாறு கேட்டுக்கொள்கிறோம்

ஆய்வின் நோக்கம்:

குழந்தைகளில் தைராக்ஸின் மாத்திரையை வழக்கமாக காலையில் கொடுப்பதற்கு பதிலாக இரவில் கொடுப்பதால் தைராய்டு ஹார்மோன் அளவில் ஏற்படும் மாற்றங்கள் பற்றி அறிய ஆய்வு மேற்கொள்ளப்படுகிறது.

செய்முறை

உங்கள் குழந்தையிடம் இதயத்துடிப்பு, உயரம் மற்றும் எடை அளவிடப்படுகின்றது. மற்றும் 5 மிலி இரத்தம் எடுத்து தைராய்டு ஹார்மோன் அளவு, கொழுப்புச்சத்து அளவு மற்றும் உப்பு அளவினை கண்டறிவோம்.

ஆய்வில் பங்கேற்க மறுத்தால்

இந்த ஆய்வில் பங்கேற்பது முற்றிலும் உங்களது சொந்த விருப்பமே தாங்கள் எப்பொழுது வேண்டுமானாலும் இவ்வாராய்ச்சியிலிருந்து விலகிக் கொள்ளலாம். தாங்கள் விலகி கொள்வதால் உங்கள் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்தவித மாற்றமோ, பாதிப்போ இருக்காது.

பங்கேற்பதின் இலாப நஷ்டங்கள்

இந்த ஆய்வில் இருந்து பெறப்படும் தகவல்கள் நம் நாட்டை நோயில்லாத நாடாக மாற்ற உபயோகப்படும். இவ்வாறு நாட்டின் வளர்ச்சியில் பங்கேற்ற பெருமை உங்களையும், உங்கள் குழந்தையையும் சேரும்.

இரகசியத்தன்மை

ஆய்வில் இருந்து பெறப்படும் தகவல்கள் வெளியிடப்படும்பொழுது உங்கள் மற்றும் உங்கள் குழந்தையின் அடையாளம் இரகசியமாக வைக்கப்படும்.

பங்கேற்பவர் உரிமை

இந்த ஆய்வைப் பற்றி மேலும தகவல் அறிய தொடர்பு கொள்ள வேண்டிய நபர்

முதன்மை ஆராய்ச்சியாளர்	:	ஆர்.இராதாகிருஷ்ணன்
கைபேசி எண்	:	9629596767
முகவரி	:	இரண்டாம் ஆண்டு, முதுநிலை மருத்துவ மாணவர் அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8.

இடம்:

தேதி: பெற்றோர் கையொப்பம்

ஒப்புதல் படிவம்

ஆராய்ச்சி நடத்தப்படும் இடம் : அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-8

முதன்மை ஆராய்ச்சியாளர் : மரு. ஆர்.ராதாகிருஷ்ணன்

பங்கேற்பவர் பெயர் : வயது பாலினம்

மருத்துவமனை எண்:

ஆய்வின் தலைப்பு : குழந்தைகளுக்கு தைராக்ஸின் மாத்திரையை வழக்கமாக காலையில் கொடுப்பதற்கு பதில் இரவில் கொடுப்பதால் ஏற்படும் மாற்றங்கள் பற்றிய ஆய்வு

1) எனக்கு தரப்பட்ட ஆராய்ச்சியில் பங்கு பெறுவோர்க்கான தகவல் படிவத்தை முழுவதுமாக படித்து புரிந்து கொண்டேன்.
2) ஆராய்ச்சியின் தன்மை முழுவதுமாகவும் விரிவாகவும் எடுத்துரைக்கப்பட்டது. எனது கேள்விகளுக்கு விடையளிக்கப்பட்டது.
3) ஆய்வாளர் என் உரிமைகளையும், பொறுப்புகளையும் நன்கு விளக்கினார்.
4) நான் எனது குழந்தை ஆய்வாளருக்கு முழு ஒத்துழைப்பு கொடுக்கவும், பரிசோதனை செய்து கொள்ளவும் அனுமதிக்கிறேன்.
5) எனது குழந்தை ஆராய்ச்சியில் பங்கேற்பதால் ஏற்படும் சாதக பாதகங்களை விளக்கப்பட்டன.
6) நான் எப்பொழுது வேண்டுமானாலும் எனது குழந்தையை இந்த ஆராய்ச்சியிலிருந்து விலக்கிக் கொள்ளலாம் என்று எனக்கு எடுத்துரைக்கப்பப்பட்டது. அவ்வாறு விலகிக்கொள்வதால் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்த மாற்றமும் இருக்காது என அறிந்து கொண்டேன்.
7) இந்த ஆய்வில் என் குழந்தையிடமிருந்து பெறப்படும் மருத்துவ தகவலை ஆய்விதழிலிலோ, கருத்தரங்கிலோ வெளியிடுவதில் எனக்கு எந்தவித ஆட்சேபணையும் இல்லை.

8) அவ்வாறு வெளியிடப்படும்போது என் குழந்தையின் தன் அடையாளங்களை வெளியிடப்பட மாட்டாது என எனக்கு உறுதியளிக்கப்பட்டது.
9) எனக்கு இந்த ஆராய்ச்சி குறித்து எதுவும் சந்தேகம் இருந்தால் உடனே ஆராய்ச்சியாளரை கேட்டு தெளிவுப்படுத்திக் கொள்ளலாம் என தெரிவிக்கப்பட்டது.
10) இந்த ஒப்புதல் படிவத்தில் கையொப்பமிடுவதின் மூலம் இந்த படிவத்தில் உள்ளவை யாவும் எனக்கு தெளிவாக எடுத்துரைக்கப்பட்டு அதை நான் நன்கு புரிந்துக்கொண்டேன் என தெரிவித்துக்கொள்கிறேன்.

நோயாளியின் பெற்றோர் / பாதுகாவலர்

பெயர்: .... கையொப்பம்: ....
தேதி:

ஆராய்ச்சியாளர்

பெயர்: .... கையொப்பம்: ....
தேதி:

சாட்சி 1.

பெயர்: .... கையொப்பம்: ....
தேதி:

சாட்சி 2:

பெயர்: .... கையொப்பம்: ....
தேதி:

slno	name	age	sex	endono	tsh_0	ft4_0	Urea_0	creat_0	cholest_0	tgl_0	hdl_0	ht_0	wt_0	bmi_0	hr_0	sbp_0	dbp_0	tsh_6
1	YAMINI	10.16	2	823/14	0.33	1.16	25	0.7	100	57	30	-0.06	-0.18	-0.23	99	-1.37	0.76	0.02
2	PRIYADH	7.16	2	746/15	1.2	1.27	23	0.6	171	54	48	-0.39	0.31	0.71	72	0.46	0.92	1.4
3	KAVYA	5.16	2	959/3	0.8	1.12	25	0.7	121	44	40	-0.09	0.93	1.46	103	-0.34	0	1.83
4	HARSHIT	6.83	2	891/15	2.28	1.23	22	0.7	166	57	46	-0.57	0.72	1.37	118	-0.46	0.96	3.12
5	MD.SAIF	4.66	1	492/12	1.21	1.49	24	0.6	179	63	52	-0.83	0.14	1.01	99	0.45	-0.04	0.9
6	MOHANA	6.66	2	259/14	1.08	1.6	20	0.6	136	49	48	-0.57	0.16	0.67	97	1.65	-1.52	2.63
7	SAMUVE	9.5	1	548/12	4.2	1.1	21	0.4	176	60	67	-1.43	0.63	1.63	104	-0.33	-0.33	0.4
8	MOURISH	7.33	2	225/15	0.23	2.06	17	0.6	181	42	45	-0.22	0.41	0.73	87	0.97	-1.08	0.11
9	VINODHI	5.33	2	766/13	1.39	1.64	23	0.6	172	67	44	0.6	0.81	0.76	90	0.33	-0.57	1.42
10	SWETHA	12.16	2	324/15	2.7	0.83	25	0.7	165	59	50	-0.72	-0.61	-0.35	105	-0.6	-0.01	1.9
11	DIVYADH	8.16	2	565/14	1.31	1.56	26	0.6	200	58	39	-0.21	-0.09	-0.017	86	0.62	-0.39	0.88
12	KAVIPRI	8.33	2	740/15	1.44	1.42	22	0.6	160	47	49	0.096	0.36	0.41	101	-0.48	1.37	2.1
13	VENKET	11.16	1	639/12	1.59	1.55	22	0.6	151	62	41	0.96	0.46	0.13	89	0.52	-0.6	2.34
14	DEVI	9.5	2	884/15	3.1	1.55	23	0.7	110	57	43	0.23	0.71	0.78	106	-0.85	-0.71	0.05
15	SANDHIY	10.16	2	756/15	0.02	1.72	21	0.6	109	60	54	-0.49	-0.42	-0.27	86	-0.32	-0.18	1.84
16	KAVYA	4.16	2	259/13	0.5	1.07	20	0.5	142	58	62	-0.43	0.24	0.72	108	0.44	-1.12	4.8
17	ASHWINI	3.16	2	120/15	0.38	1.54	23	0.6	176	58	51	-0.61	0.79	1.68	97	0.58	-0.25	0.86
18	DEEPA	10.83	2	219/15	3.08	1.38	25	0.5	162	52	68	-0.61	-0.75	-0.63	84	-0.09	-0.97	0.9
19	VIGNESH	9.33	1	776/07	1.34	1.58	25	0.5	103	74	50	-0.69	0.07	0.58	90	-0.86	-0.76	2.1
20	PAVITHR	9.33	2	785/15	0.69	1.37	17	0.6	157	58	51	-0.2	0.31	0.52	92	-1.16	0.18	0.12
21	MONIKA	11.16	2	967/15	2.38	1.12	18	0.6	267	53	51	-0.59	-0.14	0.16	80	0.04	0.9	3.9
22	MURALI	10.16	1	278/08	4.2	1.42	21	0.7	105	44	52	-0.44	0.31	0.69	116	0.42	-0.09	3.8
23	REVATH	10.83	2	954/15	2.16	1.81	26	0.7	121	53	59	-0.04	-0.07	-0.07	108	0.09	1.45	3.1
24	PRAJITH	6.5	1	653/10	4.7	0.84	22	0.6	167	66	48	-0.58	-0.05	0.36	92	-0.21	-0.14	3.9
25	NIZANI	6.5	2	710/15	1.4	0.9	28	0.6	177	60	46	0.25	1.27	1.62	95	-0.44	-0.1	2.1
26	GOPIKA	10.33	2	862/15	0.24	1.52	22	0.6	148	49	49	0.08	0.06	0.018	97	-0.34	-0.09	5.93
27	HARINI	12.33	2	829/13	2.1	1.79	20	0.6	186	53	50	0.31	-0.47	-0.77	102	1.53	0.02	0.4
28	NAFIZA	10.33	2	730/13	0.37	1.02	23	0.6	155	50	58	0.08	0.47	0.55	69	-0.4	0.58	0.8
29	NANDHI	11.33	2	724/11	3.9	0.82	28	0.4	132	58	60	-0.43	-0.21	-0.01	95	-0.45	-0.39	1.95
30	POOJA	11.5	2	873/15	0.63	1.32	22	0.7	176	59	63	-0.58	-0.33	-0.07	84	-0.51	-0.5	1.4
31	MONISH	12.5	2	675/09	1.21	0.9	24	0.5	162	43	41	-0.48	-1.12	-1.16	99	-0.39	-0.27	2.4
32	AKASTH	7.5	2	910/15	2.4	1.74	23	0.6	170	57	39	0.2	0.23	0.16	104	0.96	-0.14	3.7
33	VASANT	11.5	2	760/15	1.45	1.42	26	0.6	156	56	47	0.15	-0.54	-0.8	77	1.05	0.55	5.1
34	BANUPR	11.66	2	833/07	3.3	1.5	26	0.6	132	44	37	-1.5	-0.53	0.23	68	0.06	0.72	5.4
35	GOKILA	12.5	2	636/15	2.8	1.16	32	0.6	174	62	56	-1.41	-0.57	0.11	85	0.32	1.02	2.1
36	DEBORA	11.5	1	743/15	0.26	1.48	25	0.5	147	64	50	-0.84	-0.9	-0.7	92	-0.51	-0.93	0.9

37	DHANUS	11.66	1	908/13	0.42	1.34	18	0.7	165	59	55	-0.19	-0.49	-0.55	103	1.65	-1.11	2.5
38	KARTHIC	12.5	1	581/10	2.72	1.6	20	0.5	154	62	60	-0.177	-0.22	-0.2	89	0.69	-0.43	2.8
39	HANITHA	12.66	2	816/15	2.8	1.7	23	0.8	156	45	45	0.4	-0.67	-1.08	95	0.07	-1.34	3.1
40	SANGEET	11.83	2	931/15	0.24	1.42	19	0.7	179	54	53	1.07	-0.65	-1.49	94	-1.18	0.32	1.1
41	BHUVAN	12.83	2	717/14	4.9	1.04	26	0.5	149	58	50	-1.24	-0.98	0.48	85	0.67	-0.21	2.9
42	ROJA	3.33	2	134/16	5.2	1.1	20	0.7	152	52	57	0.42	-0.24	-0.56	98	1.57	0.3	1
43	NANDHI	7.66	2	128/11	3.32	1.4	24	0.6	135	53	54	0.25	0.59	0.64	105	-0.11	0.73	1.7
44	VANITHA	8.5	2	539/15	0.08	1.99	25	0.7	164	74	35	-0.05	0.26	0.37	89	1.57	-0.61	0.07
45	PRIYANK	8.66	2	379/14	3.7	1.66	24	0.5	152	39	41	0.01	0.25	0.3	96	0.99	0.08	1.9
46	YASHWA	7.83	2	644/15	0.05	2.09	30	0.6	169	51	44	-0.09	0.3	0.47	85	-0.59	-0.19	0.9
47	AISHWAI	8.83	2	902/15	0.01	2.07	21	0.7	190	47	63	0.54	-0.11	-0.59	93	1.16	0.48	0.5
48	TAMILM	7.5	1	425/08	1.15	1.88	16	0.5	144	60	67	-0.25	0.55	0.96	99	-0.03	0.19	1.37
49	DINESH I	8.16	1	756/15	5.27	1.131	21	0.7	158	45	59	-0.69	-0.71	-0.47	93	0.9	-1.47	1.9
50	SANJAY I	8.33	1	160/16	3.53	1.39	27	0.5	158	42	77	-0.35	0.53	1.03	104	-0.54	-1	3.9
51	NANDHI	10.5	2	292/15	2.4	1.6	25	0.6	142	53	42	-0.48	-0.12	0.12	88	-1.71	-0.71	2.5
52	ARCHAN	10.5	2	882/15	1.07	1.13	16	0.4	164	71	48	-0.12	-0.31	-0.35	100	-1.04	0.93	5.2
53	DIVYA	10.66	2	85/04	2.87	1.04	29	0.7	134	60	41	-0.009	-0.09	-0.13	116	-0.79	1.29	6.1
54	KALAIVA	10.66	2	170/15	2.86	1.32	23	0.7	140	47	44	-1.04	-0.64	-0.2	106	-0.1	0.65	4.2
55	SUBIKSH	9.16	2	762/14	2.36	1.4	23	0.5	145	50	43	-0.35	-0.13	0.01	105	-0.32	1.74	1.9
56	SABARIN	10.16	1	186/04	0.5	1.8	22	0.3	152	50	63	-0.39	-0.35	-0.31	92	-1.18	-0.88	1.02
57	HARINAT	10.5	1	275/14	4.68	1.02	24	0.5	160	71	51	0.04	-0.25	-0.38	103	0.09	-0.37	2.4
58	N ANDHI	3.5	2	231/14	5.1	1.09	27	0.5	112	55	68	-1.23	-0.24	0.77	97	-0.62	-0.95	5
59	HEMALA	3.66	2	495/15	0.65	1.28	24	0.8	121	62	48	-0.83	0.079	0.86	93	0.67	-0.72	0.6
60	BHUVAN	3.83	2	885/15	0.05	1.73	27	0.7	105	57	38	-0.47	-0.28	-0.01	99	1.33	-0.81	0.06
61	VIGNESH	3.16	2	166/14	1.53	1.13	23	0.5	113	56	54	-0.62	0.17	0.83	96	-1.42	0.94	1.99
62	ASRAF A	4.5	1	780/12	0.89	1.27	15	0.7	161	41	52	-0.03	-0.01	0.0009	87	0.05	-0.08	0.7
63	DAKSHA	3.5	1	116/14	1.5	1.4	27	0.6	142	50	56	-0.23	0.13	0.39	99	-1.22	1.46	1.01
64	GAYATH	6.5	2	20/11	0.58	1.57	33	0.6	161	69	51	-1.45	-0.26	0.77	93	0.16	-0.39	1.4
65	SRINITH	5.5	2	962/15	0.61	1.22	24	0.6	156	45	42	1.27	1.53	1.4	106	-0.83	-1.26	0.9
66	PRIYADH	6.33	2	698/12	1.1	1.5	25	0.6	148	46	63	0.17	0.5	0.61	89	-0.31	0.16	1.9
67	MUKESH	4.33	1	161/14	2.71	1.4	33	0.6	114	36	58	-0.81	0.21	1.12	94	0.11	0.04	4.9
68	KADHAR	5.16	1	673/15	3.1	1.4	27	0.7	134	50	52	-0.32	0.06	0.29	103	0.07	0.32	3.5
69	GOKUL	5.33	1	645/10	3.2	1.5	30	0.5	148	36	70	-0.22	-0.01	0.06	90	0.7	-0.11	3.9
70	SATHISH	6.16	1	18/12	4.2	1.32	21	0.8	142	38	51	0.03	0.51	0.62	108	0.09	-0.92	4.4
71	PRATHIS	5.5	1	928/15	3.7	1.21	24	0.7	143	58	41	-1.42	-0.87	-0.03	93	-1.83	0.95	4.9
72	SURYA	8.5	1	77/10	4.8	1.33	27	0.5	152	50	48	-0.79	-0.35	0.13	98	0.58	0.53	6.4
73	MOHAN	9.16	1	86/11	3.9	1.4	28	0.6	154	39	61	-0.64	-0.06	0.37	93	-1.15	0	0.7
74	RANJITH	10.5	1	87/11	4.01	1.39	29	0.4	156	66	36	-1.54	-0.19	0.67	103	0.65	1.59	2.9
75	TEJASRE	6.16	2	92/16	3.2	1.5	24	0.7	140	52	64	1.09	1.4	1.41	100	1.18	-0.1	2.8
76	SURESH	4.16	1	293/15	5.1	1.07	29	0.8	160	53	44	0.13	1.08	1.51	86	-1.75	-0.98	4.6
77	MAHESH	5.66	1	352/16	4.9	1.1	24	0.6	135	71	46	-0.12	-0.01	-0.02	96	-0.09	-0.34	3.2

ft4_6	urea_6	Creat_6	cholest_6	Tgl_6	hdl_6	hr_6	sbp_6	dbp_6	tsh_12	ft4_12	urea_12	Creat_12	cholest_12	Tgl_12	Hdl_12	ht_12	wt_12	bmi_12	hr_12	sbp_12	dbp_12
1.5	25	0.7	131	58	41	97	0.71	-0.55	0.05	1.6	23	0.6	105	57	55	-0.09	-0.26	-0.31	74	0.44	-0.29
1.3	24	0.6	132	57	59	88	-0.34	-0.78	0.9	1.4	14	0.6	166	52	52	-0.42	0.26	0.65	94	-0.59	-0.89
1.84	20	0.7	161	48	64	105	-0.92	-0.82	0.66	1.1	18	0.6	120	50	42	-0.13	0.87	1.4	85	1.68	1.84
1.21	25	0.7	140	62	32	106	-0.88	1	0.82	1.4	21	0.7	150	57	55	-0.6	0.66	1.3	91	0.66	0.3
1.79	28	0.6	182	55	51	73	-0.76	1.36	0.05	1.6	25	0.6	128	50	61	-0.9	0.13	1.05	98	-1	-0.38
1.43	22	0.6	169	56	37	98	-1.29	-0.27	1.3	1.5	25	0.5	140	42	47	-0.6	0.13	0.63	93	0.22	0.24
1.02	26	0.4	140	42	70	92	-0.89	0.75	4.6	0.9	23	0.6	150	61	58	-1.42	0.57	1.54	115	-1.89	-0.27
2.08	19	0.6	152	43	52	101	-1.1	0.55	0.05	1.8	25	0.5	182	53	40	-0.26	0.36	0.67	91	0.58	0.12
1.7	29	0.6	125	61	59	109	0.52	-0.38	1.3	1.03	22	0.5	170	53	65	0.56	0.76	0.72	89	1.73	-0.34
0.81	26	0.7	164	60	48	109	0.01	0.26	1.2	0.9	24	0.6	160	41	57	-0.69	-0.66	-0.43	96	0.24	-0.03
1.2	25	0.6	174	36	49	100	0.59	-0.88	0.9	1.3	20	0.6	190	45	56	-0.24	-0.14	-0.06	84	0.11	1.19
1.1	21	0.6	161	45	54	81	-1.29	0.04	3	1.01	21	0.7	170	52	45	-0.05	0.3	0.42	95	0.64	-1.29
1.46	27	0.6	125	54	61	102	-0.71	-0.7	3	1.2	17	0.7	150	60	60	0.93	0.42	0.05	86	-0.72	0
0.08	25	0.7	172	54	44	102	-0.32	-0.15	0.14	1.7	23	0.6	108	70	55	0.19	0.63	0.69	89	-0.47	1
1.54	26	0.6	165	53	68	102	-0.4	-0.5	3.4	1.4	25	0.6	170	68	58	-0.52	-0.49	-0.35	100	0.74	-0.12
1.2	26	0.5	155	53	54	95	-0.29	-0.89	3.62	1.3	26	0.6	152	32	56	-0.52	0.21	0.76	109	-0.78	0.54
1.48	26	0.6	188	56	48	103	1.21	-0.81	1.5	1.5	22	0.6	178	49	56	-0.71	0.72	1.68	97	0.39	0.4
1.1	23	0.5	149	49	55	105	-0.93	-1.06	3.4	1.4	22	0.6	150	54	50	-0.63	-0.79	-0.66	116	-0.59	-0.19
1.3	32	0.5	151	50	57	103	1.68	-0.1	2.5	1.3	23	0.4	118	48	72	-0.69	0.03	0.51	96	0.81	-0.91
1.32	26	0.6	117	44	61	106	-0.24	0.8	2.21	0.9	21	0.7	152	45	56	-0.24	0.23	0.44	97	-0.81	0.49
1.21	24	0.6	135	59	43	113	-0.91	0.73	4.9	1.1	20	0.5	200	54	51	-0.6	-0.22	0.035	97	0.93	0.52
1.3	20	0.7	119	58	53	110	1.58	-0.07	1.1	1.2	23	0.6	130	62	42	-0.45	0.25	0.61	98	0.06	0.34
1.5	24	0.7	171	56	54	116	0.76	0.37	3.5	1.4	25	0.6	140	55	51	-0.067	-0.15	-0.15	105	-0.92	0.01
0.9	29	0.6	112	66	42	100	0.98	0.28	1.96	0.98	25	0.6	170	40	64	-0.61	-0.08	0.34	93	-0.47	-0.72
1.08	27	0.6	125	59	49	89	-1.23	-0.91	3	1.4	17	0.6	154	43	58	0.21	1.21	1.54	92	-0.36	0.43
1.17	22	0.6	159	55	58	81	-0.44	0.67	5.2	1.2	18	0.5	152	44	47	0.08	-0.01	-0.08	95	-1.3	-1.22
1.21	24	0.6	147	45	33	106	-0.15	-1.1	0.9	1.002	21	0.7	190	68	51	0.32	-0.54	-0.86	96	1.59	0.71
1.12	22	0.6	141	40	64	93	0.67	0.33	1.4	0.92	26	0.5	162	38	48	0.05	0.38	0.46	105	0.94	0.81
0.89	26	0.4	161	34	48	92	-0.76	0.89	1.4	0.9	22	0.8	135	55	56	-0.47	-0.28	-0.08	107	-0.29	-1.3
1.2	26	0.7	141	52	56	89	0.49	-0.22	3.5	1.22	28	0.7	174	57	57	-0.58	-0.4	-0.16	111	-0.12	0.15
1.01	20	0.5	121	53	64	117	-0.89	0.03	4.4	0.98	22	0.5	160	62	41	-0.43	-1.16	-1.23	86	0.08	-0.42
1.06	25	0.6	171	57	64	105	-0.77	0.29	4.95	1.04	20	0.7	138	58	55	0.16	0.18	0.11	84	0.44	-0.77
1.44	25	0.6	149	46	48	105	0.19	-0.53	2.3	1.5	23	0.6	160	65	54	0.15	-0.6	-0.88	93	-1.78	-1.38
1.1	20	0.6	149	65	73	96	-0.76	1.05	1	0.8	28	0.7	160	68	42	-1.5	-0.59	0.15	81	-0.05	-0.33
1.12	27	0.6	118	62	45	92	0.28	1.08	0.8	1.1	22	0.5	168	53	60	-1.37	-0.61	0.03	102	-0.93	-0.15
1.52	28	0.5	128	63	74	102	-0.97	0.77	1.9	1.51	24	0.6	140	44	62	-0.86	-0.94	-0.76	95	0.22	-0.89

1.43	26	0.7	146	40	58	98	-0.82	-0.38	1.3	1.28	23	0.7	148	40	57	-0.22	-0.54	-0.61	102	0.63	0.28
1.5	27	0.5	166	62	58	93	0.79	1.01	2.2	1.4	26	0.5	154	70	60	-0.29	-0.27	-0.21	107	-1.56	-0.79
1.68	20	0.8	193	46	61	97	0.57	0.36	3.4	1.59	26	0.7	158	56	43	0.46	-0.71	-1.15	90	-1.56	-0.55
1.5	24	0.7	189	55	45	93	1.45	1.59	1.4	1.5	32	0.5	169	72	52	1.08	-0.71	-1.56	99	-0.85	-1.52
1.01	26	0.5	96	38	51	110	0.67	0.72	0.8	1.02	25	0.6	170	59	56	-1.18	-1.02	-0.58	96	-0.32	-1.04
1.5	23	0.7	138	62	47	115	0.24	0.11	3.4	1.6	18	0.4	172	65	50	0.41	-0.31	-0.64	104	0.53	-0.48
1.4	24	0.6	152	47	47	106	-0.28	-0.62	4.6	1.3	20	0.7	143	50	51	0.21	0.53	0.57	100	-0.56	-1.24
2.04	32	0.7	137	47	57	104	-0.49	-0.66	0.1	1.75	23	0.7	178	43	72	-0.09	0.2	0.3	80	-0.04	-0.66
1.52	18	0.5	129	70	50	93	0.68	-0.6	0.9	1.51	19	0.5	160	83	37	-0.02	0.18	0.23	86	-0.13	1.03
2.01	23	0.6	152	55	57	85	0.36	-0.03	0.81	1.9	26	0.3	156	58	49	-0.12	0.24	0.41	89	-0.89	0.59
1.98	21	0.7	172	69	63	106	-0.44	-0.37	0.82	1.6	20	0.5	194	49	45	0.5	-0.17	-0.64	110	0.13	0.58
1.72	26	0.5	155	55	50	88	0.32	0.48	2.49	1.5	24	0.5	144	57	58	-0.28	0.48	0.89	114	0.75	0.16
1.03	21	0.7	116	47	54	85	-0.77	1.04	0.9	1.02	25	0.8	157	51	43	-0.7	-0.75	-0.5	106	-0.52	0.68
1.1	19	0.5	122	58	44	91	-0.26	0.87	5.4	1.2	24	0.7	165	55	40	-0.36	0.47	0.95	126	-0.01	-0.41
1.2	24	0.6	126	51	48	109	-0.48	-0.35	1.4	1.4	30	0.5	150	50	51	-0.51	-0.2	0.04	87	-0.87	0.58
1.1	31	0.4	189	71	39	101	-0.65	1.17	3	1.09	21	0.7	148	54	69	-0.15	-0.39	-0.43	93	-0.27	0.78
1.03	27	0.7	111	46	57	104	0.24	0	0.8	1.1	16	0.6	187	69	58	-0.03	-0.17	-0.21	86	0.27	-0.4
1.31	21	0.7	154	53	55	108	0.34	-1.48	2.4	1.4	21	0.6	156	38	45	-1.06	-0.72	-0.28	89	-0.22	-1.63
1.3	22	0.5	160	37	60	97	0.38	-0.09	3.78	1.2	27	0.6	131	54	48	-0.35	-0.13	0.01	88	0.62	-1.17
1.7	23	0.3	173	50	56	103	-0.69	-0.61	1.4	1.6	25	0.6	158	66	48	-0.36	-0.43	-0.37	110	-0.6	-0.5
1.01	31	0.5	161	61	57	107	0.54	1.52	0.68	1.1	16	0.6	164	53	69	0.022	-0.3	-0.45	97	0.29	-0.61
0.9	24	0.5	182	58	45	112	1.53	0.65	1	1.01	29	0.7	112	61	53	-1.29	-0.25	0.8	116	1.62	-0.26
1.3	27	0.8	190	64	51	84	-1.37	0.43	1	1.2	23	0.5	98	59	60	-0.89	0.05	0.87	93	0.82	0.01
1.74	25	0.7	150	63	57	122	0.52	0.18	0.08	1.7	23	0.8	112	52	55	-0.52	-0.29	0.026	82	0.74	1.09
1.21	25	0.5	127	65	63	97	0.39	0.54	1.5	1.23	22	0.7	155	43	54	-0.69	0.17	0.9	100	-0.31	-1.72
1.3	19	0.7	115	54	66	78	-0.19	0.44	4.2	1.5	24	0.5	158	60	39	-0.122	-0.015	0.06	99	0.54	-0.9
1.41	23	0.6	193	57	55	82	0.76	-0.4	0.8	1.7	27	0.6	150	61	48	-0.35	0.12	0.51	102	0.11	0.03
1.34	30	0.6	156	60	59	88	0.02	-1.04	1.4	1.31	24	0.4	154	58	67	-1.46	-0.28	0.73	97	-0.21	-0.79
1.48	20	0.6	198	56	62	104	-1.68	-0.93	1.1	1.33	27	0.7	152	54	43	1.24	1.46	1.32	86	0.27	0.75
1.4	21	0.6	165	50	39	83	-0.04	0.39	3.64	1.2	23	0.8	148	45	44	0.13	0.45	0.56	110	0.01	-1.09
1.01	17	0.6	180	58	49	114	-0.54	1.52	4.8	1.01	15	0.6	138	59	34	-0.88	0.21	1.17	105	-0.72	0.42
1.5	23	0.7	143	53	55	110	-1.18	0.23	3.46	1.3	27	0.6	158	39	48	-0.36	0.01	0.27	98	0.24	0.1
1.3	17	0.5	123	43	53	88	0.84	-0.72	5.1	1.2	33	0.7	155	63	34	-0.26	0	0.08	118	-0.22	0.09
1.21	17	0.8	228	51	62	94	-0.21	0.03	4.6	1.1	24	0.5	148	64	36	0	0.44	0.59	97	0.81	0.5
1.3	25	0.7	162	64	40	88	-0.5	-0.59	2.2	1.2	25	0.5	152	38	56	-1.42	-0.87	-0.03	86	-0.57	-1.8
1.28	23	0.5	140	61	59	96	-0.29	-0.17	3.59	1.42	33	0.7	154	56	48	-0.8	-0.38	0.07	94	-0.15	0.74
1.25	18	0.6	160	61	55	77	0.9	0.59	2.1	1.3	27	0.5	154	49	37	-0.66	-0.07	0.36	108	0.55	0.84
1.8	29	0.4	143	45	61	110	1.36	-0.86	2.34	1.7	30	0.6	159	44	64	-1.55	-0.24	0.6	81	-0.51	-0.26
1.6	23	0.7	156	67	57	108	0.36	1.04	1.6	1.8	21	0.5	131	37	50	1.04	1.4	1.34	111	0.96	0.71
1.5	23	0.8	141	51	60	127	1.36	-0.46	2.32	1.62	24	0.7	135	50	51	0.15	1	1.48	90	-0.25	-0.63
1.6	31	0.6	151	42	60	88	0.84	0.04	2.45	1.53	27	0.5	138	52	69	-0.16	-0.04	-0.02	92	0.18	-0.28

slno	name	age	sex	endono	tsh_0	ft4_0	Urea_0	creat_0	cholest_0	tgl_0	hdl_0	ht_0	wt_0	bmi_0	hr_0	sbp_0	dbp_0	tsh_6
1	YAMINI	10.16	2	823/14	0.33	1.16	25	0.7	100	57	30	-0.06	-0.18	-0.23	99	-1.37	0.76	0.02
2	PRIYADH	7.16	2	746/15	1.2	1.27	23	0.6	171	54	48	-0.39	0.31	0.71	72	0.46	0.92	1.4
3	KAVYA	5.16	2	959/3	0.8	1.12	25	0.7	121	44	40	-0.09	0.93	1.46	103	-0.34	0	1.83
4	HARSHIT	6.83	2	891/15	2.28	1.23	22	0.7	166	57	46	-0.57	0.72	1.37	118	-0.46	0.96	3.12
5	MD.SAIF	4.66	1	492/12	1.21	1.49	24	0.6	179	63	52	-0.83	0.14	1.01	99	0.45	-0.04	0.9
6	MOHANA	6.66	2	259/14	1.08	1.6	20	0.6	136	49	48	-0.57	0.16	0.67	97	1.65	-1.52	2.63
7	SAMUVE	9.5	1	548/12	4.2	1.1	21	0.4	176	60	67	-1.43	0.63	1.63	104	-0.33	-0.33	0.4
8	MOURISH	7.33	2	225/15	0.23	2.06	17	0.6	181	42	45	-0.22	0.41	0.73	87	0.97	-1.08	0.11
9	VINODHI	5.33	2	766/13	1.39	1.64	23	0.6	172	67	44	0.6	0.81	0.76	90	0.33	-0.57	1.42
10	SWETHA	12.16	2	324/15	2.7	0.83	25	0.7	165	59	50	-0.72	-0.61	-0.35	105	-0.6	-0.01	1.9
11	DIVYADH	8.16	2	565/14	1.31	1.56	26	0.6	200	58	39	-0.21	-0.09	-0.017	86	0.62	-0.39	0.88
12	KAVIPRI	8.33	2	740/15	1.44	1.42	22	0.6	160	47	49	0.096	0.36	0.41	101	-0.48	1.37	2.1
13	VENKET	11.16	1	639/12	1.59	1.55	22	0.6	151	62	41	0.96	0.46	0.13	89	0.52	-0.6	2.34
14	DEVI	9.5	2	884/15	3.1	1.55	23	0.7	110	57	43	0.23	0.71	0.78	106	-0.85	-0.71	0.05
15	SANDHIY	10.16	2	756/15	0.02	1.72	21	0.6	109	60	54	-0.49	-0.42	-0.27	86	-0.32	-0.18	1.84
16	KAVYA	4.16	2	259/13	0.5	1.07	20	0.5	142	58	62	-0.43	0.24	0.72	108	0.44	-1.12	4.8
17	ASHWINI	3.16	2	120/15	0.38	1.54	23	0.6	176	58	51	-0.61	0.79	1.68	97	0.58	-0.25	0.86
18	DEEPA	10.83	2	219/15	3.08	1.38	25	0.5	162	52	68	-0.61	-0.75	-0.63	84	-0.09	-0.97	0.9
19	VIGNESH	9.33	1	776/07	1.34	1.58	25	0.5	103	74	50	-0.69	0.07	0.58	90	-0.86	-0.76	2.1
20	PAVITHR	9.33	2	785/15	0.69	1.37	17	0.6	157	58	51	-0.2	0.31	0.52	92	-1.16	0.18	0.12
21	MONIKA	11.16	2	967/15	2.38	1.12	18	0.6	267	53	51	-0.59	-0.14	0.16	80	0.04	0.9	3.9
22	MURALI	10.16	1	278/08	4.2	1.42	21	0.7	105	44	52	-0.44	0.31	0.69	116	0.42	-0.09	3.8
23	REVATH	10.83	2	954/15	2.16	1.81	26	0.7	121	53	59	-0.04	-0.07	-0.07	108	0.09	1.45	3.1
24	PRAJITH	6.5	1	653/10	4.7	0.84	22	0.6	167	66	48	-0.58	-0.05	0.36	92	-0.21	-0.14	3.9
25	NIZANI	6.5	2	710/15	1.4	0.9	28	0.6	177	60	46	0.25	1.27	1.62	95	-0.44	-0.1	2.1
26	GOPIKA	10.33	2	862/15	0.24	1.52	22	0.6	148	49	49	0.08	0.06	0.018	97	-0.34	-0.09	5.93
27	HARINI	12.33	2	829/13	2.1	1.79	20	0.6	186	53	50	0.31	-0.47	-0.77	102	1.53	0.02	0.4
28	NAFIZA	10.33	2	730/13	0.37	1.02	23	0.6	155	50	58	0.08	0.47	0.55	69	-0.4	0.58	0.8
29	NANDHI	11.33	2	724/11	3.9	0.82	28	0.4	132	58	60	-0.43	-0.21	-0.01	95	-0.45	-0.39	1.95
30	POOJA	11.5	2	873/15	0.63	1.32	22	0.7	176	59	63	-0.58	-0.33	-0.07	84	-0.51	-0.5	1.4
31	MONISH	12.5	2	675/09	1.21	0.9	24	0.5	162	43	41	-0.48	-1.12	-1.16	99	-0.39	-0.27	2.4
32	AKASTH	7.5	2	910/15	2.4	1.74	23	0.6	170	57	39	0.2	0.23	0.16	104	0.96	-0.14	3.7
33	VASANT	11.5	2	760/15	1.45	1.42	26	0.6	156	56	47	0.15	-0.54	-0.8	77	1.05	0.55	5.1
34	BANUPR	11.66	2	833/07	3.3	1.5	26	0.6	132	44	37	-1.5	-0.53	0.23	68	0.06	0.72	5.4
35	GOKILA	12.5	2	636/15	2.8	1.16	32	0.6	174	62	56	-1.41	-0.57	0.11	85	0.32	1.02	2.1
36	DEBORA	11.5	1	743/15	0.26	1.48	25	0.5	147	64	50	-0.84	-0.9	-0.7	92	-0.51	-0.93	0.9

37	DHANUS	11.66	1	908/13	0.42	1.34	18	0.7	165	59	55	-0.19	-0.49	-0.55	103	1.65	-1.11	2.5
38	KARTHIC	12.5	1	581/10	2.72	1.6	20	0.5	154	62	60	-0.177	-0.22	-0.2	89	0.69	-0.43	2.8
39	HANITHA	12.66	2	816/15	2.8	1.7	23	0.8	156	45	45	0.4	-0.67	-1.08	95	0.07	-1.34	3.1
40	SANGEET	11.83	2	931/15	0.24	1.42	19	0.7	179	54	53	1.07	-0.65	-1.49	94	-1.18	0.32	1.1
41	BHUVAN	12.83	2	717/14	4.9	1.04	26	0.5	149	58	50	-1.24	-0.98	0.48	85	0.67	-0.21	2.9
42	ROJA	3.33	2	134/16	5.2	1.1	20	0.7	152	52	57	0.42	-0.24	-0.56	98	1.57	0.3	1
43	NANDHI	7.66	2	128/11	3.32	1.4	24	0.6	135	53	54	0.25	0.59	0.64	105	-0.11	0.73	1.7
44	VANITHA	8.5	2	539/15	0.08	1.99	25	0.7	164	74	35	-0.05	0.26	0.37	89	1.57	-0.61	0.07
45	PRIYANK	8.66	2	379/14	3.7	1.66	24	0.5	152	39	41	0.01	0.25	0.3	96	0.99	0.08	1.9
46	YASHWA	7.83	2	644/15	0.05	2.09	30	0.6	169	51	44	-0.09	0.3	0.47	85	-0.59	-0.19	0.9
47	AISHWAI	8.83	2	902/15	0.01	2.07	21	0.7	190	47	63	0.54	-0.11	-0.59	93	1.16	0.48	0.5
48	TAMILM	7.5	1	425/08	1.15	1.88	16	0.5	144	60	67	-0.25	0.55	0.96	99	-0.03	0.19	1.37
49	DINESH I	8.16	1	756/15	5.27	1.131	21	0.7	158	45	59	-0.69	-0.71	-0.47	93	0.9	-1.47	1.9
50	SANJAY I	8.33	1	160/16	3.53	1.39	27	0.5	158	42	77	-0.35	0.53	1.03	104	-0.54	-1	3.9
51	NANDHI	10.5	2	292/15	2.4	1.6	25	0.6	142	53	42	-0.48	-0.12	0.12	88	-1.71	-0.71	2.5
52	ARCHAN	10.5	2	882/15	1.07	1.13	16	0.4	164	71	48	-0.12	-0.31	-0.35	100	-1.04	0.93	5.2
53	DIVYA	10.66	2	85/04	2.87	1.04	29	0.7	134	60	41	-0.009	-0.09	-0.13	116	-0.79	1.29	6.1
54	KALAIVA	10.66	2	170/15	2.86	1.32	23	0.7	140	47	44	-1.04	-0.64	-0.2	106	-0.1	0.65	4.2
55	SUBIKSH	9.16	2	762/14	2.36	1.4	23	0.5	145	50	43	-0.35	-0.13	0.01	105	-0.32	1.74	1.9
56	SABARIN	10.16	1	186/04	0.5	1.8	22	0.3	152	50	63	-0.39	-0.35	-0.31	92	-1.18	-0.88	1.02
57	HARINAT	10.5	1	275/14	4.68	1.02	24	0.5	160	71	51	0.04	-0.25	-0.38	103	0.09	-0.37	2.4
58	N ANDHI	3.5	2	231/14	5.1	1.09	27	0.5	112	55	68	-1.23	-0.24	0.77	97	-0.62	-0.95	5
59	HEMALA	3.66	2	495/15	0.65	1.28	24	0.8	121	62	48	-0.83	0.079	0.86	93	0.67	-0.72	0.6
60	BHUVAN	3.83	2	885/15	0.05	1.73	27	0.7	105	57	38	-0.47	-0.28	-0.01	99	1.33	-0.81	0.06
61	VIGNESH	3.16	2	166/14	1.53	1.13	23	0.5	113	56	54	-0.62	0.17	0.83	96	-1.42	0.94	1.99
62	ASRAF A	4.5	1	780/12	0.89	1.27	15	0.7	161	41	52	-0.03	-0.01	0.0009	87	0.05	-0.08	0.7
63	DAKSHA	3.5	1	116/14	1.5	1.4	27	0.6	142	50	56	-0.23	0.13	0.39	99	-1.22	1.46	1.01
64	GAYATH	6.5	2	20/11	0.58	1.57	33	0.6	161	69	51	-1.45	-0.26	0.77	93	0.16	-0.39	1.4
65	SRINITH	5.5	2	962/15	0.61	1.22	24	0.6	156	45	42	1.27	1.53	1.4	106	-0.83	-1.26	0.9
66	PRIYADH	6.33	2	698/12	1.1	1.5	25	0.6	148	46	63	0.17	0.5	0.61	89	-0.31	0.16	1.9
67	MUKESH	4.33	1	161/14	2.71	1.4	33	0.6	114	36	58	-0.81	0.21	1.12	94	0.11	0.04	4.9
68	KADHAR	5.16	1	673/15	3.1	1.4	27	0.7	134	50	52	-0.32	0.06	0.29	103	0.07	0.32	3.5
69	GOKUL	5.33	1	645/10	3.2	1.5	30	0.5	148	36	70	-0.22	-0.01	0.06	90	0.7	-0.11	3.9
70	SATHISH	6.16	1	18/12	4.2	1.32	21	0.8	142	38	51	0.03	0.51	0.62	108	0.09	-0.92	4.4
71	PRATHIS	5.5	1	928/15	3.7	1.21	24	0.7	143	58	41	-1.42	-0.87	-0.03	93	-1.83	0.95	4.9
72	SURYA	8.5	1	77/10	4.8	1.33	27	0.5	152	50	48	-0.79	-0.35	0.13	98	0.58	0.53	6.4
73	MOHAN	9.16	1	86/11	3.9	1.4	28	0.6	154	39	61	-0.64	-0.06	0.37	93	-1.15	0	0.7
74	RANJITH	10.5	1	87/11	4.01	1.39	29	0.4	156	66	36	-1.54	-0.19	0.67	103	0.65	1.59	2.9
75	TEJASRE	6.16	2	92/16	3.2	1.5	24	0.7	140	52	64	1.09	1.4	1.41	100	1.18	-0.1	2.8
76	SURESH	4.16	1	293/15	5.1	1.07	29	0.8	160	53	44	0.13	1.08	1.51	86	-1.75	-0.98	4.6
77	MAHESH	5.66	1	352/16	4.9	1.1	24	0.6	135	71	46	-0.12	-0.01	-0.02	96	-0.09	-0.34	3.2

ft4_6	urea_6	Creat_6	cholest_6	Tgl_6	hdl_6	hr_6	sbp_6	dbp_6	tsh_12	ft4_12	urea_12	Creat_12	cholest_12	Tgl_12	Hdl_12	ht_12	wt_12	bmi_12	hr_12	sbp_12	dbp_12
1.5	25	0.7	131	58	41	97	0.71	-0.55	0.05	1.6	23	0.6	105	57	55	-0.09	-0.26	-0.31	74	0.44	-0.29
1.3	24	0.6	132	57	59	88	-0.34	-0.78	0.9	1.4	14	0.6	166	52	52	-0.42	0.26	0.65	94	-0.59	-0.89
1.84	20	0.7	161	48	64	105	-0.92	-0.82	0.66	1.1	18	0.6	120	50	42	-0.13	0.87	1.4	85	1.68	1.84
1.21	25	0.7	140	62	32	106	-0.88	1	0.82	1.4	21	0.7	150	57	55	-0.6	0.66	1.3	91	0.66	0.3
1.79	28	0.6	182	55	51	73	-0.76	1.36	0.05	1.6	25	0.6	128	50	61	-0.9	0.13	1.05	98	-1	-0.38
1.43	22	0.6	169	56	37	98	-1.29	-0.27	1.3	1.5	25	0.5	140	42	47	-0.6	0.13	0.63	93	0.22	0.24
1.02	26	0.4	140	42	70	92	-0.89	0.75	4.6	0.9	23	0.6	150	61	58	-1.42	0.57	1.54	115	-1.89	-0.27
2.08	19	0.6	152	43	52	101	-1.1	0.55	0.05	1.8	25	0.5	182	53	40	-0.26	0.36	0.67	91	0.58	0.12
1.7	29	0.6	125	61	59	109	0.52	-0.38	1.3	1.03	22	0.5	170	53	65	0.56	0.76	0.72	89	1.73	-0.34
0.81	26	0.7	164	60	48	109	0.01	0.26	1.2	0.9	24	0.6	160	41	57	-0.69	-0.66	-0.43	96	0.24	-0.03
1.2	25	0.6	174	36	49	100	0.59	-0.88	0.9	1.3	20	0.6	190	45	56	-0.24	-0.14	-0.06	84	0.11	1.19
1.1	21	0.6	161	45	54	81	-1.29	0.04	3	1.01	21	0.7	170	52	45	-0.05	0.3	0.42	95	0.64	-1.29
1.46	27	0.6	125	54	61	102	-0.71	-0.7	3	1.2	17	0.7	150	60	60	0.93	0.42	0.05	86	-0.72	0
0.08	25	0.7	172	54	44	102	-0.32	-0.15	0.14	1.7	23	0.6	108	70	55	0.19	0.63	0.69	89	-0.47	1
1.54	26	0.6	165	53	68	102	-0.4	-0.5	3.4	1.4	25	0.6	170	68	58	-0.52	-0.49	-0.35	100	0.74	-0.12
1.2	26	0.5	155	53	54	95	-0.29	-0.89	3.62	1.3	26	0.6	152	32	56	-0.52	0.21	0.76	109	-0.78	0.54
1.48	26	0.6	188	56	48	103	1.21	-0.81	1.5	1.5	22	0.6	178	49	56	-0.71	0.72	1.68	97	0.39	0.4
1.1	23	0.5	149	49	55	105	-0.93	-1.06	3.4	1.4	22	0.6	150	54	50	-0.63	-0.79	-0.66	116	-0.59	-0.19
1.3	32	0.5	151	50	57	103	1.68	-0.1	2.5	1.3	23	0.4	118	48	72	-0.69	0.03	0.51	96	0.81	-0.91
1.32	26	0.6	117	44	61	106	-0.24	0.8	2.21	0.9	21	0.7	152	45	56	-0.24	0.23	0.44	97	-0.81	0.49
1.21	24	0.6	135	59	43	113	-0.91	0.73	4.9	1.1	20	0.5	200	54	51	-0.6	-0.22	0.035	97	0.93	0.52
1.3	20	0.7	119	58	53	110	1.58	-0.07	1.1	1.2	23	0.6	130	62	42	-0.45	0.25	0.61	98	0.06	0.34
1.5	24	0.7	171	56	54	116	0.76	0.37	3.5	1.4	25	0.6	140	55	51	-0.067	-0.15	-0.15	105	-0.92	0.01
0.9	29	0.6	112	66	42	100	0.98	0.28	1.96	0.98	25	0.6	170	40	64	-0.61	-0.08	0.34	93	-0.47	-0.72
1.08	27	0.6	125	59	49	89	-1.23	-0.91	3	1.4	17	0.6	154	43	58	0.21	1.21	1.54	92	-0.36	0.43
1.17	22	0.6	159	55	58	81	-0.44	0.67	5.2	1.2	18	0.5	152	44	47	0.08	-0.01	-0.08	95	-1.3	-1.22
1.21	24	0.6	147	45	33	106	-0.15	-1.1	0.9	1.002	21	0.7	190	68	51	0.32	-0.54	-0.86	96	1.59	0.71
1.12	22	0.6	141	40	64	93	0.67	0.33	1.4	0.92	26	0.5	162	38	48	0.05	0.38	0.46	105	0.94	0.81
0.89	26	0.4	161	34	48	92	-0.76	0.89	1.4	0.9	22	0.8	135	55	56	-0.47	-0.28	-0.08	107	-0.29	-1.3
1.2	26	0.7	141	52	56	89	0.49	-0.22	3.5	1.22	28	0.7	174	57	57	-0.58	-0.4	-0.16	111	-0.12	0.15
1.01	20	0.5	121	53	64	117	-0.89	0.03	4.4	0.98	22	0.5	160	62	41	-0.43	-1.16	-1.23	86	0.08	-0.42
1.06	25	0.6	171	57	64	105	-0.77	0.29	4.95	1.04	20	0.7	138	58	55	0.16	0.18	0.11	84	0.44	-0.77
1.44	25	0.6	149	46	48	105	0.19	-0.53	2.3	1.5	23	0.6	160	65	54	0.15	-0.6	-0.88	93	-1.78	-1.38
1.1	20	0.6	149	65	73	96	-0.76	1.05	1	0.8	28	0.7	160	68	42	-1.5	-0.59	0.15	81	-0.05	-0.33
1.12	27	0.6	118	62	45	92	0.28	1.08	0.8	1.1	22	0.5	168	53	60	-1.37	-0.61	0.03	102	-0.93	-0.15
1.52	28	0.5	128	63	74	102	-0.97	0.77	1.9	1.51	24	0.6	140	44	62	-0.86	-0.94	-0.76	95	0.22	-0.89

1.43	26	0.7	146	40	58	98	-0.82	-0.38	1.3	1.28	23	0.7	148	40	57	-0.22	-0.54	-0.61	102	0.63	0.28
1.5	27	0.5	166	62	58	93	0.79	1.01	2.2	1.4	26	0.5	154	70	60	-0.29	-0.27	-0.21	107	-1.56	-0.79
1.68	20	0.8	193	46	61	97	0.57	0.36	3.4	1.59	26	0.7	158	56	43	0.46	-0.71	-1.15	90	-1.56	-0.55
1.5	24	0.7	189	55	45	93	1.45	1.59	1.4	1.5	32	0.5	169	72	52	1.08	-0.71	-1.56	99	-0.85	-1.52
1.01	26	0.5	96	38	51	110	0.67	0.72	0.8	1.02	25	0.6	170	59	56	-1.18	-1.02	-0.58	96	-0.32	-1.04
1.5	23	0.7	138	62	47	115	0.24	0.11	3.4	1.6	18	0.4	172	65	50	0.41	-0.31	-0.64	104	0.53	-0.48
1.4	24	0.6	152	47	47	106	-0.28	-0.62	4.6	1.3	20	0.7	143	50	51	0.21	0.53	0.57	100	-0.56	-1.24
2.04	32	0.7	137	47	57	104	-0.49	-0.66	0.1	1.75	23	0.7	178	43	72	-0.09	0.2	0.3	80	-0.04	-0.66
1.52	18	0.5	129	70	50	93	0.68	-0.6	0.9	1.51	19	0.5	160	83	37	-0.02	0.18	0.23	86	-0.13	1.03
2.01	23	0.6	152	55	57	85	0.36	-0.03	0.81	1.9	26	0.3	156	58	49	-0.12	0.24	0.41	89	-0.89	0.59
1.98	21	0.7	172	69	63	106	-0.44	-0.37	0.82	1.6	20	0.5	194	49	45	0.5	-0.17	-0.64	110	0.13	0.58
1.72	26	0.5	155	55	50	88	0.32	0.48	2.49	1.5	24	0.5	144	57	58	-0.28	0.48	0.89	114	0.75	0.16
1.03	21	0.7	116	47	54	85	-0.77	1.04	0.9	1.02	25	0.8	157	51	43	-0.7	-0.75	-0.5	106	-0.52	0.68
1.1	19	0.5	122	58	44	91	-0.26	0.87	5.4	1.2	24	0.7	165	55	40	-0.36	0.47	0.95	126	-0.01	-0.41
1.2	24	0.6	126	51	48	109	-0.48	-0.35	1.4	1.4	30	0.5	150	50	51	-0.51	-0.2	0.04	87	-0.87	0.58
1.1	31	0.4	189	71	39	101	-0.65	1.17	3	1.09	21	0.7	148	54	69	-0.15	-0.39	-0.43	93	-0.27	0.78
1.03	27	0.7	111	46	57	104	0.24	0	0.8	1.1	16	0.6	187	69	58	-0.03	-0.17	-0.21	86	0.27	-0.4
1.31	21	0.7	154	53	55	108	0.34	-1.48	2.4	1.4	21	0.6	156	38	45	-1.06	-0.72	-0.28	89	-0.22	-1.63
1.3	22	0.5	160	37	60	97	0.38	-0.09	3.78	1.2	27	0.6	131	54	48	-0.35	-0.13	0.01	88	0.62	-1.17
1.7	23	0.3	173	50	56	103	-0.69	-0.61	1.4	1.6	25	0.6	158	66	48	-0.36	-0.43	-0.37	110	-0.6	-0.5
1.01	31	0.5	161	61	57	107	0.54	1.52	0.68	1.1	16	0.6	164	53	69	0.022	-0.3	-0.45	97	0.29	-0.61
0.9	24	0.5	182	58	45	112	1.53	0.65	1	1.01	29	0.7	112	61	53	-1.29	-0.25	0.8	116	1.62	-0.26
1.3	27	0.8	190	64	51	84	-1.37	0.43	1	1.2	23	0.5	98	59	60	-0.89	0.05	0.87	93	0.82	0.01
1.74	25	0.7	150	63	57	122	0.52	0.18	0.08	1.7	23	0.8	112	52	55	-0.52	-0.29	0.026	82	0.74	1.09
1.21	25	0.5	127	65	63	97	0.39	0.54	1.5	1.23	22	0.7	155	43	54	-0.69	0.17	0.9	100	-0.31	-1.72
1.3	19	0.7	115	54	66	78	-0.19	0.44	4.2	1.5	24	0.5	158	60	39	-0.122	-0.015	0.06	99	0.54	-0.9
1.41	23	0.6	193	57	55	82	0.76	-0.4	0.8	1.7	27	0.6	150	61	48	-0.35	0.12	0.51	102	0.11	0.03
1.34	30	0.6	156	60	59	88	0.02	-1.04	1.4	1.31	24	0.4	154	58	67	-1.46	-0.28	0.73	97	-0.21	-0.79
1.48	20	0.6	198	56	62	104	-1.68	-0.93	1.1	1.33	27	0.7	152	54	43	1.24	1.46	1.32	86	0.27	0.75
1.4	21	0.6	165	50	39	83	-0.04	0.39	3.64	1.2	23	0.8	148	45	44	0.13	0.45	0.56	110	0.01	-1.09
1.01	17	0.6	180	58	49	114	-0.54	1.52	4.8	1.01	15	0.6	138	59	34	-0.88	0.21	1.17	105	-0.72	0.42
1.5	23	0.7	143	53	55	110	-1.18	0.23	3.46	1.3	27	0.6	158	39	48	-0.36	0.01	0.27	98	0.24	0.1
1.3	17	0.5	123	43	53	88	0.84	-0.72	5.1	1.2	33	0.7	155	63	34	-0.26	0	0.08	118	-0.22	0.09
1.21	17	0.8	228	51	62	94	-0.21	0.03	4.6	1.1	24	0.5	148	64	36	0	0.44	0.59	97	0.81	0.5
1.3	25	0.7	162	64	40	88	-0.5	-0.59	2.2	1.2	25	0.5	152	38	56	-1.42	-0.87	-0.03	86	-0.57	-1.8
1.28	23	0.5	140	61	59	96	-0.29	-0.17	3.59	1.42	33	0.7	154	56	48	-0.8	-0.38	0.07	94	-0.15	0.74
1.25	18	0.6	160	61	55	77	0.9	0.59	2.1	1.3	27	0.5	154	49	37	-0.66	-0.07	0.36	108	0.55	0.84
1.8	29	0.4	143	45	61	110	1.36	-0.86	2.34	1.7	30	0.6	159	44	64	-1.55	-0.24	0.6	81	-0.51	-0.26
1.6	23	0.7	156	67	57	108	0.36	1.04	1.6	1.8	21	0.5	131	37	50	1.04	1.4	1.34	111	0.96	0.71
1.5	23	0.8	141	51	60	127	1.36	-0.46	2.32	1.62	24	0.7	135	50	51	0.15	1	1.48	90	-0.25	-0.63
1.6	31	0.6	151	42	60	88	0.84	0.04	2.45	1.53	27	0.5	138	52	69	-0.16	-0.04	-0.02	92	0.18	-0.28

slno	name	age	sex	endono	tsh_0	ft4_0	urea_0	creat_0	cholest_0	tgl_0	hdl_0	ht_0	wt_0	bmi_0	hr_0	sbp_0	dbp_0	tsh_6	ft4_6	urea_6	Creat_6	cholest_6	tgl_6	hdl_6	hr_6	sbp_6	dbp_6	tsh_12
1	HARINI	10.66	2	885/15	1.58	1.51	18	0.5	141	57	50	-0.19	-0.41	-0.44	88	0.15	0.78	3.37	1.68	25	0.6	170	65	65	117	0.4	-0.26	2.44
2	SWETHA	7.16	2	827/13	0.48	1.19	23	0.6	158	52	34	0.41	0.71	0.71	88	-0.95	-1.38	1.42	1.14	23	0.7	165	47	49	112	-0.28	1.44	2.1
3	BHARATHI	5.16	2	241/10	2.68	1.18	19	0.5	158	56	44	-0.51	0.53	1.22	99	-0.86	1.04	2.7	1.85	25	0.5	146	69	32	99	0.83	0.87	3.5
4	MONISHA	5.33	2	892/15	1.6	1.22	20	0.7	106	50	50	-0.45	0.007	0.42	92	0.59	-0.67	1.1	1.29	22	0.5	122	36	56	96	-0.09	-0.1	3.8
5	AKASH	4.33	1	896/11	2.07	1.65	25	0.5	159	54	34	-0.95	-0.23	0.58	108	0.48	-0.49	2.5	1.47	24	0.7	168	38	32	85	-0.3	0.37	3.1
6	GOMATHI	5.5	2	213/13	1.5	1.4	29	0.7	160	44	62	-0.09	0.43	0.74	103	-1.4	-0.19	1.2	1.36	20	0.5	169	37	60	92	0.98	1.35	3.4
7	JEYAPRAKASH	9.16	1	266/08	2.4	1.43	24	0.6	162	45	55	-0.71	-0.06	0.42	91	-0.71	-1.61	0.74	2	21	0.6	163	60	46	98	-0.2	0.95	0.9
8	SATHYAPRIYA	7.33	2	535/14	1.4	1.59	31	0.5	148	37	64	-0.38	0.09	0.4	96	-0.03	-0.71	4.1	1.79	17	0.5	152	50	59	112	-0.03	-0.66	3.2
9	AFRIN BANU	4.5	2	177/13	0.012	2.4	23	0.5	139	50	62	-0.91	0.13	1.009	86	0.03	-0.14	0.5	1.42	23	0.7	128	48	52	102	1.13	1.49	0.7
10	MAMTHA	12.5	2	266/13	1.1	1.21	24	0.6	150	56	50	-0.35	-0.98	-1.04	101	-0.1	-1.62	3.9	1.6	25	0.5	166	60	58	103	0.37	-0.95	2.1
11	PRIYADHARSHIN	8.83	2	108/08	0.18	1.81	24	0.4	147	59	52	0.39	0.23	0.03	104	-0.05	0.88	0.3	1.97	26	0.7	112	92	65	92	0.57	0.43	0.5
12	PAVITHRA	8.66	2	689/15	0.62	1.49	24	0.8	132	49	34	-0.66	0.49	1.05	100	0.18	0.27	0.17	1.82	22	0.6	175	50	49	92	-0.65	-0.03	0.22
13	SAKTHIVEL	11.5	1	849/06	3.2	1.89	27	0.7	157	48	50	-0.2	-0.37	-0.38	86	-0.39	1.09	2.9	1.21	22	0.5	178	66	58	98	0.51	-0.34	2.4
14	PRIYADHARSHIN	10.5	2	884/15	0.01	2.12	22	0.6	143	51	56	-0.62	0.11	0.51	104	-0.32	0.88	0.03	2.02	23	0.5	110	58	53	88	1.64	0.19	0.5
15	DEVADHARSHIN	10.83	2	881/15	0.02	1.3	21	0.6	165	47	57	-0.61	-0.01	0.34	101	-0.79	-0.2	0.4	1.1	21	0.6	157	47	55	96	0.52	-0.73	0.5
16	DHANUSHKA	3.16	2	621/15	1.9	1.2	23	0.6	150	44	55	0.15	-0.01	-0.2	97	0.41	-0.04	3.1	1.62	20	0.4	138	62	71	108	0.48	0.59	2.4
17	RITHIKA	3.33	2	222/15	0.1	1.63	23	0.7	168	50	48	-0.18	0.1	0.28	110	0.35	-1.56	0.16	1.45	23	0.8	127	48	52	100	-0.33	0.56	0.4
18	SALOMI	11.16	2	573/13	0.32	0.83	27	0.3	144	56	51	0.11	-0.17	-0.29	95	0.19	-0.2	0.33	1.33	25	0.7	107	61	51	100	-1.43	-0.59	0.35
19	MD.NEEZAMUDEE	8.5	1	279/13	0.78	1.78	28	0.6	151	56	62	-0.65	0.1	0.65	96	0.93	0.35	0.8	1.53	25	0.6	141	43	54	104	-0.37	0.51	0.75
20	SANDHIYA RANI	8.5	2	192/15	3.13	1.18	29	0.5	134	38	54	0.17	0.23	0.17	82	0.43	0.46	3.24	1.19	17	0.6	147	50	71	97	0.62	0.45	3.09
21	YUVASHREE	11.33	2	113/03	1.12	1.3	19	0.6	154	40	45	-0.29	-0.24	-0.134	90	0.05	0.28	1.24	1.68	18	0.6	123	59	54	97	-0.63	-0.52	1.12
22	LOGESH	9.33	1	731/12	4.25	1.38	18	0.7	132	47	55	-0.54	0.016	0.41	83	-0.76	-0.38	3.2	1.67	21	0.7	161	61	51	104	-1.1	0.89	3.3
23	PRIYADHARSHIN	11.5	2	268/11	1.4	0.97	22	0.4	125	60	40	-0.141	-0.41	-0.45	103	-1.12	-0.13	3.2	1.24	26	0.3	126	53	51	92	0	-0.7	2.4
24	ARAVANAPRAKA	7.16	1	203/09	0.45	1.75	17	0.3	162	49	46	-0.45	0.37	0.83	81	-1.58	0.86	0.35	1.65	22	0.6	134	43	47	94	0.86	0.09	0.15
25	DHANALAKSHM	6.83	2	137/10	3.1	1.4	26	0.5	148	65	56	-0.57	-0.06	0.34	85	-0.15	0.17	2.89	1.63	28	0.5	103	39	57	-0.78	-0.78	0.3	1.87
26	ABINAYA	10.66	2	879/11	3.56	1.38	23	0.6	157	49	56	-0.69	-0.83	-0.69	99	-0.05	-0.6	3.12	1.27	22	0.6	118	54	44	100	0.3	0.16	2.56
27	SASIKALA	11.66	2	952/15	0.12	1.57	26	0.7	160	44	57	-0.25	-0.26	-0.18	94	0.2	0.31	0.23	1.79	20	0.7	136	59	60	105	-0.21	-0.4	0.3
28	JOTHI	12.83	2	424/15	0.08	1.03	28	0.5	154	52	60	0.48	-0.79	-1.28	92	-0.68	-1.02	0.1	1.2	23	0.4	112	55	60	92	0.23	0.5	0.3
29	KALAIVANI	11.83	2	749/10	1.27	1.41	21	0.6	152	64	51	0.059	-0.19	-0.26	99	0.92	-0.5	4.1	1.49	28	0.3	131	51	55	104	0.09	-0.88	3.2
30	JAISAI	12.66	2	351/14	4.8	1.41	24	0.6	156	50	51	0.13	-0.98	-1.33	92	0.61	0.33	3.6	1.57	22	0.5	186	49	61	97	-0.42	0.12	2.5
31	CHINNARASU	12.5	1	926/15	2	1.4	23	0.5	158	53	52	0.1	-0.44	-0.69	84	0.71	0.31	4.2	1.52	24	0.6	171	50	51	88	-0.38	-0.73	3.3
32	YOGESH	12.16	1	581/10	0.3	1.7	26	0.6	154	53	56	0.2	-0.35	-0.61	103	-1.14	0.43	0.5	1.31	23	0.7	171	73	52	73	0.38	0.8	0.2
33	ANITHA	12.5	2	87/11	3.25	1.5	25	0.7	148	59	54	-0.06	-0.64	-0.76	95	0.67	0.74	2.9	1.65	26	0.5	157	49	60	99	-0.56	0.31	2.5
34	AGASTHIYA	11.16	2	931/15	2.42	1.6	17	0.5	154	60	33	-0.11	-0.74	-0.94	95	-0.67	-0.12	2.1	1.13	26	0.6	174	48	46	84	0.24	-1.32	1.9
35	SUJA	11.33	2	932/15	1.27	1	19	0.6	167	75	59	1	-0.32	-1.02	83	0.06	-0.13	2.2	1.5	32	0.6	139	48	47	111	1.48	-1.22	1.8
36	SWETHA	12.33	2	529/13	1.27	1	20	0.5	167	56	42	-0.51	-0.57	-0.42	87	-1.3	-0.04	1.14	1.19	25	0.5	171	49	68	87	1.26	-0.03	1.03
37	DHARANI	11.5	2	159/06	1.92	1.42	29	0.6	165	39	51	-1.11	-0.64	-0.14	94	0.66	0.35	1.72	1.76	18	0.6	177	66	51	99	-0.7	0.23	1.53
38	SUGANTHI	11.66	2	699/12	1.93	1.01	30	0.6	166	44	53	-0.95	-0.56	-0.14	102	-0.57	0.16	1.5	1.58	20	0.7	139	67	55	116	-0.54	1.15	1.3
39	DIVYA	12.16	2	881/07	2.87	1.04	27	0.6	134	51	53	-0.49	-0.93	-0.91	112	-0.59	-1.71	2.4	0.97	23	0.5	99	55	50	80	1.09	1.78	1.9

40	VASUKI	11.83	2	963/15	4.11	1.25	35	0.7	153	42	54	0.11	-0.38	-0.55	110	1.32	0.58	3.98	1	19	0.6	114	58	50	113	-0.42	0.21	2.7
41	SEVANTHI	11.5	2	334/15	2.9	1.4	20	0.5	157	58	45	-1.52	-0.47	0.33	74	0.07	-0.89	2.1	1.45	26	0.5	136	48	56	104	1.7	-0.27	1.6
42	PAVITHRA	7.5	2	598/10	1.2	0.8	22	0.6	121	45	62	-0.62	-0.43	-0.17	91	1.22	-0.1	2.4	1.55	20	0.6	132	75	56	107	1.75	0.51	3.4
43	KEERTHANA	8.33	2	865/15	3.14	1.8	19	0.8	151	53	43	-0.05	0.09	0.14	96	0.1	0.11	1.58	1.89	24	0.6	144	63	54	97	-0.52	-1.6	1.42
44	ASHWITHA	8.16	2	13/15	0.27	1.5	20	0.7	132	56	67	-0.67	-0.49	-0.22	90	-0.57	0.08	0.05	2.16	25	0.6	152	55	54	82	-0.42	-1.68	0.14
45	RAMYA	7.66	2	231/16	1.3	1.07	20	0.7	162	55	60	-0.66	-0.7	-0.51	87	0.35	0.19	5.9	1.54	24	0.7	187	39	46	93	0.63	-1.3	4.2
46	TEENESH	7.5	1	688/13	5.2	1.01	29	0.6	164	70	46	-0.59	-0.47	-0.21	96	-0.25	-0.63	6.01	1.36	30	0.5	90	62	43	106	0.73	-1.09	4.9
47	KARTHICK	8.5	1	997/15	2.27	1.131	24	0.7	158	47	58	-1.61	0.1	1.23	104	1.39	0.85	4.8	1.65	21	0.6	123	74	50	97	-0.27	-0.93	2.84
48	SIVASHANKAR	8.33	1	165/16	4.2	1.04	31	0.6	145	34	48	-0.75	0.77	1.55	97	-0.62	-0.77	5.5	0.86	16	0.8	153	53	45	104	-0.52	0.19	5.5
49	PAVITHRA	10.5	2	912/15	0.57	0.98	22	0.6	165	45	60	0.23	0.72	0.8	82	-0.04	1.37	7.2	0.71	21	0.7	126	74	54	107	0.12	-0.31	2.1
50	RASIYA	9.16	2	822/13	5.82	0.99	18	0.6	176	61	44	-0.59	0.19	0.61	85	-1.33	0.68	4.99	0.97	27	0.7	177	66	49	90	-0.25	0.09	0.13
51	INDHUMATHI	10.33	2	742/15	2.2	1.23	25	0.6	188	56	53	0.08	-0.86	-1.3	86	-0.34	-0.51	6.8	1.05	25	0.6	117	47	52	104	-0.2	0.39	5.9
52	KAMALI	10.16	2	13/16	1.9	0.97	24	0.5	172	33	62	0.08	0.11	0.07	110	0.52	0.5	2.2	1.11	16	0.7	166	69	53	91	0.4	-0.8	4.9
53	RESHMA	10.33	2	843/15	2.8	0.45	26	0.6	155	65	46	0.18	-0.28	-0.53	80	0.29	-0.32	5.1	1.53	29	0.6	155	54	63	111	0.48	0.6	0.4
54	ABITHA	10.16	2	856/15	0.05	3.33	23	0.6	194	52	58	1.13	0.92	0.57	97	0.83	0.73	0.4	1.34	23	0.6	155	65	47	94	0	-0.25	0.6
55	SARASWAATHI	9.5	2	832/16	0.09	1.89	19	0.7	176	52	44	-1.22	0.58	1.45	99	0.71	-0.75	0.3	1.49	23	0.6	168	47	51	109	-0.31	-1.71	0.5
56	PRAVEENKUMAR	10.5	1	316/12	0.24	1.58	29	0.5	139	48	52	-0.01	0	0.005	104	0.89	0.08	0.5	1.61	22	0.6	93	33	60	96	0	0.29	1.8
57	DHINAKARAN	9.5	1	284/12	0.62	2.17	27	0.6	168	54	35	0.05	-0.01	-0.04	100	0.02	0.86	1.8	1.16	24	0.5	176	41	62	98	-0.78	-0.17	4.2
58	SWETHA	3.5	2	243/13	0.16	1.58	24	0.7	172	60	63	-1.23	0.49	1.81	107	0.21	-0.53	0.67	1.68	27	0.6	179	44	66	100	-0.1	0.29	5.1
59	ESTHAR	3.66	2	564/13	2.8	1.3	32	0.5	104	54	64	-0.79	0.31	1.15	110	0.5	0.49	4.2	1.37	24	0.6	143	53	41	81	0.42	-1.37	0.6
60	VARSHINI	3.83	2	344/12	2.8	1.23	23	0.7	108	61	45	0.11	-0.09	-0.27	95	0.13	-0.73	1.7	0.82	27	0.7	175	50	58	104	-0.36	1.75	1.4
61	POOVESH	3.16	1	98/14	0.68	1.94	19	0.6	198	52	30	-0.75	0.17	0.96	86	-0.29	-0.01	4.2	1.57	23	0.5	132	39	40	115	-1.75	-1.48	1.9
62	VISHESH	3.5	1	981/15	2.3	1.3	22	0.6	142	30	46	-1.75	-1.47	-0.5	82	0.3	-1.5	2.9	1.39	15	0.6	143	55	72	86	-0.68	-1.31	0.4
63	JEEVA SHREE	4.16	2	735/15	4.2	1.11	28	0.6	132	62	43	-0.65	0.03	0.62	112	-0.09	0.93	5.1	1.57	27	0.7	151	46	44	111	0.44	1.09	1.02
64	JASIKA	5.5	2	65/14	3.38	1.15	17	0.7	179	77	68	-1.37	-0.18	0.89	98	-0.92	1.06	1.23	0.57	33	0.5	161	62	60	100	1.07	0.19	0.4
65	REICHAL	6.5	2	468/15	3.52	1.9	29	0.6	142	55	61	0.17	0.92	1.2	114	-0.24	-0.66	5.1	2.12	24	0.7	134	71	49	88	-0.85	1.78	1.12
66	YOGAPRIYA	6.33	2	793/14	2.2	1.7	21	0.5	133	57	40	-1.11	-0.14	-0.81	101	0.83	-1.46	2.3	0.9	25	0.6	208	36	62	97	1.3	-0.79	1.134
67	RAMANA	5.16	1	433/15	0.02	1.36	22	0.6	160	76	61	-0.66	0.53	1.1	107	0.57	-0.57	0.4	0.97	33	0.6	167	55	46	81	-1.19	-0.45	4.2
68	RAJA	6.5	1	615/15	2.02	0.96	23	0.7	128	62	53	-0.58	-0.29	0.04	92	0.58	-0.76	3.9	1.87	27	0.6	131	39	47	97	-0.47	-0.79	2.12
69	AKASH	5.33	1	780/11	0.89	1.7	16	0.6	132	70	52	-0.26	0.06	0.2	85	-0.73	1.46	1.1	1.53	30	0.7	137	56	49	97	1.39	1.33	1.3
70	SRINATH	4.5	1	577/14	4.4	1.5	20	0.7	122	47	50	-0.14	1.07	1.75	125	1.07	0.78	4.2	2.13	21	0.6	189	44	60	90	0.16	0.05	1.8
71	RAKESH	5.33	1	187/16	3	1.2	23	0.6	142	55	54	0.02	0.37	0.38	100	-0.27	-1.04	5.1	1.16	24	0.5	194	50	60	85	-0.07	-0.34	2.34
72	SURESH	8.16	1	142/14	0.8	1.4	16	0.6	167	62	54	-0.69	0.12	0.7	91	-0.99	0.78	1.01	1.29	27	0.6	153	55	44	114	1.65	0.32	1.07
73	RAMESH	9.5	1	48/16	1.2	1.65	28	0.5	174	63	57	0.04	0.75	1.03	99	0.87	0.07	1.07	1.16	28	0.7	177	55	49	93	1.07	-1.01	0.8
74	RAVI	10.16	1	44/15	0.78	1.87	25	0.5	169	66	45	-0.29	0.71	1.12	93	-0.57	0.01	0.65	1.96	29	0.6	155	63	58	107	1.59	0.25	0.5
75	SRUTHI	6.16	2	112/16	4.8	1.21	29	0.6	142	54	71	-1.5	-1.05	-0.19	97	1.17	-0.14	3.2	1.48	24	0.7	146	55	64	111	0.89	0.01	1.1
76	BABU	4.16	1	122/15	3.2	1.09	28	0.6	155	66	59	-0.94	0.057	1	92	-1.43	0.19	1.9	1.33	29	0.6	118	31	51	103	-0.76	-0.5	0.9
77	ABINESH	5.5	1	118/16	3.9	1.12	23	0.7	152	53	41	-1.32	0.27	1.25	96	-1.27	0.19	1.6	1.58	24	0.6	148	61	52	105	-0.44	1.03	0.65

ft4_12	urea_12	Creat_12	cholest_12	Tgl_12	Hdl_12	ht_12	wt_12	bmi_12	Hr_12	sbp_12	dbp_12
1.4	16	0.6	139	41	55	-0.18	-0.49	-0.55	109	-0.26	-0.03
1.2	22	0.7	144	48	50	0.37	0.65	0.65	101	0.58	0.28
1.58	19	0.4	112	39	54	-0.55	0.49	1.17	112	0.3	-0.55
1.42	21	0.3	115	46	48	-0.49	-0.01	0.41	109	-0.78	1.71
1.59	24	0.5	156	67	52	-1.02	-0.22	0.66	96	0.01	0.46
1.6	22	0.6	134	61	42	-0.17	0.39	0.74	98	0.65	-0.64
1.6	31	0.7	157	61	43	-0.68	-0.1	0.33	79	0.08	-0.46
1.68	21	0.5	147	56	35	-0.46	0.05	0.38	96	0.58	1.13
1.9	20	0.6	142	62	48	-0.98	0.12	1.01	102	0.31	1.29
1.7	23	0.6	144	49	54	-0.3	-1.02	-1.12	104	0.08	0.03
1.76	18	0.5	145	61	57	0.35	0.16	-0.03	102	-0.65	0.76
2	23	0.6	138	64	47	-0.69	0.42	0.97	93	-0.6	0.11
1.4	19	0.7	159	49	46	-0.22	-0.42	-0.44	96	0.28	-0.18
1.9	20	0.5	150	34	49	-0.65	0.03	0.42	109	-0.35	-1.05
1.6	25	0.6	155	39	45	-0.66	-0.09	0.27	100	0.92	-0.13
1.7	29	0.5	140	48	42	-0.03	-0.04	-0.07	90	0.54	0.29
1.8	24	0.6	152	46	48	-0.34	0.07	0.39	102	-0.37	0.2
1.6	31	0.6	148	51	54	0.1	-0.25	-0.38	85	0	-0.47
1.7	23	0.6	144	54	54	-0.65	0.05	0.58	92	-0.83	0.61
1.6	24	0.7	143	68	36	0.05	0.16	0.16	102	0.37	0.04
1.7	24	0.5	145	30	38	-0.3	-0.31	-0.22	102	0.67	0.15
1.62	24	0.6	143	43	45	-0.55	-0.02	0.34	103	0.28	-0.95
1.57	27	0.8	141	54	58	-0.14	-0.48	-0.53	107	-0.82	-0.86
1.95	22	0.7	155	44	47	-0.47	0.31	0.77	96	0.61	0.59
1.7	21	0.7	146	63	63	-0.6	-0.09	0.3	96	0.41	0.48
1.69	23	0.6	154	40	47	-0.78	-0.9	-0.76	98	0.08	-1.4
1.7	23	0.7	132	59	42	-0.28	-0.33	-0.25	102	1.12	-0.71
1.8	27	0.6	150	55	50	0.54	-0.83	-1.35	100	-0.11	-0.03
1.7	28	0.6	153	55	62	0.07	-0.25	-0.35	77	-0.04	0.03
1.8	29	0.6	155	60	48	0.18	-1.02	-1.4	105	-1.09	-0.1
1.67	19	0.6	147	31	51	0.07	-0.49	-0.74	87	-0.52	-0.05
1.8	18	0.5	148	63	51	0.17	-0.4	-0.68	97	-1.03	0.18
1.6	22	0.6	145	65	57	-0.01	-0.68	-0.84	99	0.59	-0.39
1.8	17	0.6	146	51	58	-0.12	-0.81	-1.02	99	-1.22	-0.32
1.72	26	0.7	144	63	73	0.99	-0.39	-1.1	100	-0.84	-0.79
1.62	23	0.5	139	46	54	-0.47	-0.62	-0.5	90	0.22	0.41
1.51	26	0.6	150	50	37	-1.11	-0.67	-0.18	109	-0.16	0.35
1.7	28	0.7	158	54	42	-0.94	-0.62	-0.22	88	-0.35	0.19
1.6	21	0.5	140	58	49	-0.46	-0.98	-0.98	115	0.28	0.93

1.52	24	0.7	150	47	40	0.13	-0.44	-0.57	106	-0.33	0.43
1.72	23	0.6	138	75	56	-1.52	-0.53	0.24	92	-0.94	0.05
1.5	26	0.6	135	60	43	-0.65	-0.52	-0.27	104	0.57	-0.76
1.76	25	0.6	145	46	51	-0.09	0.03	0.08	94	-0.1	-1.12
1.9	17	0.7	157	48	54	-0.7	-0.53	-0.32	107	-0.09	-1.58
1.6	19	0.6	159	68	53	-0.65	-0.76	-0.59	89	-1.04	-0.15
1.54	20	0.5	155	70	68	-0.61	-0.5	-0.24	99	-0.75	-0.05
1.45	29	0.6	140	54	45	-1.61	0.05	1.15	109	-0.2	0.2
1.29	30	0.7	167	64	32	-0.87	0.66	1.48	91	0.45	-0.68
1.4	27	0.6	142	55	43	0.2	0.64	0.71	104	1.26	0.92
1.88	35	0.7	119	52	59	-0.62	0.12	0.53	89	1.14	0.61
1.36	20	0.6	157	41	54	0.005	-0.93	-1.36	98	-1.73	0.71
1.45	22	0.6	138	52	31	0.04	0.02	0	79	-0.42	-1.14
1.7	19	0.5	136	58	63	0.15	-0.36	-0.6	110	-0.01	0.67
2	20	0.5	154	57	50	1.09	0.83	0.48	111	-0.46	-0.67
1.98	20	0.6	156	48	50	-1.25	0.5	1.36	90	-0.71	0.06
1.4	29	0.6	145	62	46	-0.03	-0.05	-0.06	67	-0.01	-1.3
1.7	24	0.7	160	55	52	0.05	-0.01	-0.04	91	0.62	0.66
1.23	31	0.7	174	56	58	-1.35	0.44	1.86	89	0.09	-0.57
1.8	22	0.6	98	42	52	-0.84	0.27	1.14	116	-1.09	-0.59
1.6	18	0.6	102	43	59	0.01	0.11	0.05	108	-0.91	1.32
1.7	25	0.5	147	61	50	-0.88	0.17	1.09	85	-0.79	0.07
1.8	24	0.6	144	60	28	-1.82	-1.4	-0.3	108	1.14	1.22
1.6	26	0.7	142	36	60	-0.68	0.013	0.61	99	-1.25	0.1
1.9	23	0.6	162	45	75	-1.39	-0.2	0.82	98	0.06	-0.57
1.8	19	0.5	132	54	53	0.13	0.86	1.13	96	0.26	0.35
1.6	29	0.7	128	54	55	-1.13	-0.17	-0.85	100	0.66	-0.25
1.28	27	0.7	137	53	74	-0.7	0.5	1.08	100	0.29	1.39
1.62	24	0.6	135	53	60	-0.61	-0.31	0.03	104	0.91	-0.62
1.54	32	0.7	130	56	68	-0.3	0.047	0.209	91	1.16	-0.04
1.72	23	0.6	128	49	45	-0.23	1.03	1.75	119	-0.06	-1.33
1.63	19	0.6	135	50	53	-0.02	0.34	0.38	106	-0.77	-0.34
1.59	22	0.5	163	44	60	-0.75	0.04	0.64	86	-1.13	0.52
1.79	28	0.5	143	59	61	0	0.68	0.95	101	1.26	0.29
1.75	17	0.5	157	58	64	-0.36	0.64	1.05	74	0.13	0.83
1.7	29	0.7	132	56	52	-1.52	-1.04	-0.17	105	1.42	0.71
1.61	21	0.4	131	66	64	-1.04	0.056	1.1	120	0.39	0.89
1.76	22	0.5	128	59	51	-1.3	0.24	1.2	101	0.85	0.02